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# The Association of Macronutrients Intake with Mild Cognitive Impairment in Young and Middle-Aged Chinese Population

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## Strengths and limitations of this study

It is study focus mild cognitive impairment and diet in a relative younger population (age<65 years).

Our findings were totally different from western study because of the difference between Chinese and western diet.

The higher frequencies of vascular disease risk factors (such as diabetes, hypertension and hyperlipidemia) in participants may introduce bias towards the association between dietary and cognitive function.

Self-report dietary data highlight the common limitations of estimating accuracy of dietary reporting in large nutritional epidemiological studies.

**Abstract**

**Objective** Macronutrients are the main sources of dietary energy and high energy intake may increase the risk of cognitive impairment. The aim of this study was to explore the correlation between daily energy intake from macronutrients and cognitive function in Chinese.

**Design**: This is a retrospective cohort study. We analyzed the relationships between macronutrients intake and cognitive function. ANOVA analysis and $\chi^2$ test were used to compare the demographic characteristics, lifestyle, physical and laboratory parameters and macronutrients intake among different quartiles of % fat/energy. Multivariate logistic regression was used to identify the risk factors of MCI.

**Setting:** Beijing

**Subjects**: young and middle-aged persons (age<65 years) were collected from community. Montreal cognitive assessment (MoCA) and mini-mental state examination (MMSE) were used to evaluate cognitive function of all participants. Dietary intake was estimated by semi-quantitative food frequency questionnaires (FFQ).

**Results** Among 661 subjects, 80 (12.1%) had mild cognitive impairment (MCI), while 581(87.9%) had normal cognitive function. After adjusted for age, hyperlipidemia, education and total energy intake, the results revealed that high % fat (upper quartile: adjusted odds ratio [aOR] 3.90, 95% confidence interval [CI] 1.53-9.89, $p$=0.004), and % protein intake (upper quartile: aOR 2.77, 95% CI 1.24-6.15) were associated with increased frequency of MCI, while high % carbohydrate intake (upper quartile: aOR 0.30, 95% CI 0.12-0.72) was correlated with decreased risk of MCI.

**Conclusion** The results suggested that dietary pattern with high percentage of energy intake from fat and protein and low energy intake from carbohydrate may contribute to cognitive decline in young and middle-aged Chinese population.

**Key words:** Dietary pattern; mild cognitive impairment; macronutrients; energy intake

## Introduction

Dietary pattern and intake of nutrients have been shown to be associated with cognitive function. Mediterranean diet (MD), rich in vegetables, fruit, fresh fish and olive oil, has been proved to have beneficial effects on cognitive function [1, 2]. Similarly, two earlier studies of our group have demonstrated that diet rich in marine products, fruit, vegetables and vegetable juice could prevent cognitive decline in the elderly[3, 4]. And the long-chain omega-3 fatty acids (LC-n3-FA) and polyphenols including resveratrol, curcuminand flavonoids from these diets are likely the main nutrients beneficial to cognitive function [2, 5]. A great number of previous studies have also demonstrated that adequate dietary intake of vitamins and minerals were closely associated with decreased risk of cognitive impairment [6].However, those studies only examined the effects of different foods and micronutrients, without considering the influence of energy intake and the source of energy in the risk of developing MCI. A prospective cohort study[7] found that high average energy consumption increased the risk of cognitive impairment or dementia (OR 1.62, 95% CI 1.25-2.10) after adjustment for micronutrient, vascular disease, diabetes, smoking, BP and BMI, but it did not considered the source of energy either.

The primary determinants of total caloric intake and the largest proportion of the components of any diet are the three types of macronutrients: carbohydrates, fat and protein. The balanced ratio of carbohydrates, fat and protein was the basis of healthy diets, which ensures adequate intake of all nutrients. Up to now, however, there were limited studies that investigated the association of macronutrient (carbohydrates, fat and protein) with cognitive function. Roberts[8]*et al.* has reported that relatively high caloric intake from carbohydrates might increase the risk of MCI or dementia in elderly persons. Due to the inherent differences in Western and Chinese diets, this conclusion may not apply to Chinese population. Thus, we conducted a case-control study to explore the relationship between macronutrients and energy intake and cognitive function in a cohort of Chinese<65 years in age to control the bias of aging.

## Methods

### Participants

A retrospective cohort study was conducted in three community hospitals in Beijing, during December 1, 2015 to September 30, 2016. We recruited 1197(age<65) potentially eligible from 4360 outpatients; 777 agreed to participate (64.9% response). At last 661 participants were

including in the study after screening by Exclusion criteria: individuals with serious diseases (e.g. ,cancer, severe psychiatric disorders such as depression and schizophreni, a recent history of heart or respiratory failure, chronic liver or renal failure; n=25); individuals with conditions known to affect cognitive function (a recent history of alcohol abuse,n=43; cerebral infarction n=27; Severe brain injury, n=3); and individuals with Alzheimer's disease (AD)(n=0), Parkinson's disease(PD) (n=0) or long-term frequent intake of anti-depressants and other medications for neurological diseases(n=18). All experimental procedures were conducted in accordance with the guidelines in the Declaration of Helsinki and approved by the Ethics Committee of Capital Medical University, Beijing(No.2014SY33).All participants were fully informed of the study, signed a written consent and all had the right to terminate their participation at their willing.

**Data collection and grouping**

All data collection was performed by well-trained researchers according to the same criteria. Demographic characteristics and lifestyle were collected through face to face interviews; physical and laboratory parameters was measured using corresponding instruments. The collected data included age, gender, education, race(Han and other),work intensity, smoking (yes or no), drinking (yes or no),exercise, disease history(hypertension, diabetes), weight, height, andblood lipid levels.

Age was categorized into three ranks: <45 years old, 45~55 years old, and >55 years old. Body mass index(BMI) was calculated as weight(kg)/height$^2$($m^2$)and subsequently divided into three groups: normal(BMI 18.5~24.9kg/$m^2$), overweight(BMI 25.0~29.9kg/$m^2$) and obese(BMI $\geqslant$ 30kg/$m^2$).Educational levels were divided into three ranks: $\leq$ 6years, 7~12 years and > 12years.Work intensity was categorized into three groups: light (75% of time sitting or standing and 25% of time standing with activities, e.g. office workers, salesman, teacher), moderate(25%oftime sitting or standing and 75% of time with special occupational activities, e.g. students daily activities, motor vehicle driving, metalworking, electrical installation), and heavy(40% of time sitting or standing and 60% of time with special occupational activities, e.g. weeding, weight-bearing walking, dancing, skiing, riding a bicycle, mountain climbing, logging, manual excavation, playing basketball, mountain climbing, playing football). Exercise was defined as running, climbing, jumping rope, brisk walking, or kicking shuttle cock at least once a week, but did not include walking.

**Dietary questionnaire**

Dietary intake was estimated by using a semi-quantitative food frequency questionnaire (FFQ) which included a total of 34 items (whole grain, red meat, pork, beef, mutton, chicken, fish, legume and legume product, milk, eggs, fruit and vegetables, nuts, sugared beverages, cooking oil, etc.), consumption frequency (daily, weekly, monthly, yearly or never)and quantity of each consumption. The quantity of consumed food was estimated by using food models such as special charts and measuring rulers or cups. Then the intake of nutrients per day was calculated based on the China Food Composition Database [9]. Trained dietary interviewers helped all participants completing the FFQ to make sure the accuracy of the collected data.

**Cognitive function screening for MCI**

MoCA and MMSE were employed to evaluate cognitive function according to the standard protocols. The total score of MoCA is 30 and the cut-off for screening MCI was 13 for illiterate individuals, 19 for individuals with 1-6 years of education, and 24 for individuals with 7 or more years of education as previously described [6]. The total score of MMSE is 30. The cutoff scores for screening MCI was as following: 19 for illiterate individuals, 22 for individuals with 1-6 years of education and 26 for individuals with 7 or more years of education. The criteria has been proved to be appropriate for screening MCI in elderly Chinese people in a large population-based study[10].The screening of MCI in the present study was a combination of these two methods with the following criteria: MoCA≤13 and MMSE≥20 for illiteracy; MoCA≤19 and MMSE≥23 for subjects with 1-6 years of education; MoCA≤24 and MMSE≥27 for subjects with≥7 years of education.

**Statistical analysis**

Statistical analyses were performed using the SPSS 17.0 software (SPSS Inc., Chicago, IL, USA). Data distribution was tested for normality by visual inspection of histograms and the Shapiro-Wilk W-test. Continuous variables were presented as mean ± standard deviation (SD) or Median (Q), and categorical variables were described as frequencies (percentage).Logistic regression analysis was used to compare the demographic characteristics, lifestyle and physical and laboratory parameters between subjects with or without MCI. ANOVA analysis and rank sum test for continuous variables and Cochran-Mantel-Haenszel$\chi^2$ test for categorical variables were used to compare the demographic characteristics, lifestyle, physical and laboratory parameters and

macronutrients intake among different quartiles of % fat/energy (percentage of energy from total fat).Multivariate logistic regression was used to identify the risk factors of MCI and to estimate the risk of MCI between different quartiles of %nutrients/energy (percentage of energy from each nutrient). All statistical analyses were performed at the conventional two-tailed alpha level of 0.05.

## Results

### Subject

A total of 661 subjects were included in this study. The demographic characteristics, lifestyle, physical and laboratory parameters and their association with MCI were presented in Table 1.Of all the subjects, 303 (45.8%) were males and 358 (54.2%) were females; the average age was 48.5±7.3 years; the average BMI was 26.2±3.6 kg/m$^2$ and the overweight and obese group was 310(46.9%) and 104(15.7%), respectively; 80(12.1%) had MCI and 581(87.9%) had normal cognitive function. In addition, age, BMI, education, hypertension and hyperlipidemia were associated with higher risk of MCI. However, no significant differences in the prevalence of MCI were discovered in subjects among groups with different gender, race/ethnicity, labor intensity, aerobic exercise, smoking, drinking and diabetic status (Table1).

Table1 end of paper

We next compared the demographic characteristics, lifestyle, physical and laboratory parameters and energy intake from each macronutrient across quartiles of % fat/energy (percentage of energy from total fat). As shown in table 2, subjects in higher % fat/energy quartile had increased frequency of MCI, diabetes and hyperlipidemia and more advanced age. Lifestyle (smoking, drinking and exercise) and BMI were not significantly different across quartiles of % fat/energy. The total energy intake in the highest % fat/energy quartile was higher than that in the lowest quartile, but lower than that in the third % fat/energy quartile. Intake of protein and dietary fiber (in term of g/day or % of total energy) was increased across increasing % fat/energy quartiles, while the intake of carbohydrates was decreased as quartiles of % fat/energy raised. These data suggested that the increased dietary intake of fat may be associated the development of MCI. However, adjustment for potential bias, including age, hyperlipidemia, diabetes, was necessary to establish this correlation.

Table2 end of paper

Before analysis of the relationship between macronutrients intake and cognitive function, a multivariable logistic regression analysis was employed to identify risk factors of MCI, in which MCI status was defined as a dependent variable while BMI, age, education, hypertension, hyperlipidemia, and diabetes and energy intake were set as independent variables. As shown in table 3, age (OR1.72,95%CI1.18-2.52), hyperlipidemia (OR2.46,95%CI1.48-4.10) and total energy intake(OR1.67,95%CI1.31-2.12) were identified as risk factors of MCI, while education(OR0.54,95%CI0.31-0.94) was a protective factor for MCI. Although BMI was not statistically identified as a risk factor of MCI, a trend of increased risk of MCI was observed as BMI increased (OR1.36,95%CI0.95-1.96).

Table3 end of paper

We then explored the association of% of energy from a specific macronutrient (carbohydrates, fat and protein) with frequency of MCI, with adjustment for age, BMI, education, energy (quartiles) and hyperlipidemia. The risk of MCI was reduced in the highest quartile of% carbohydrate/energy by about 70%, while it was increased by nearly 2.48 and 2.77 folds in the third and the highest quartile of % protein/energy, respectively and by around 3.36 and 3.90foldsin the third and the highest quartile of % fat/energy, respectively (Table 4).

Table4 end of paper

**Discussion**

In this study of young and middle-aged population, high % fat/energy and % protein/energy intakes were associated with the increased prevalence of MCI. In contrast, high % carbohydrate/energy intake was correlated with a reduced risk of MCI. These findings suggested that a dietary pattern of high fat and protein intake and low carbohydrate intake may have adverse effects on the development of MCI. Therefore, a balanced dietary pattern that consists of optimal fat, protein and carbohydrate proportions may be beneficial to maintaining normal cognitive function in this population.

Our findings were in opposite to the results of a study by Robert *et al.*, which reported that dietary with relatively high caloric intake from carbohydrates and low caloric intake from fat and proteins might increase the risk of MCI [8]. This difference may stem from the difference in the age of subjects and the source of carbohydrate in diets. In the present study, participants were younger

than subjects in the study by Robert *et al.* (<65years VS 70-89 years), and dietary carbohydrates mainly came from rice and wheat flour, while carbohydrates in Roberts' study were mainly derived from sugar. In elderly persons, a dietary pattern high in simple sugars may disrupt glucose and insulin metabolism [11-14]. It is well known that glucose and insulin metabolism has a close relationship with cognitive function [15]. Thus, in younger population, fat instead of carbohydrates may represent a key factor for increased risk of MCI, because glucose and insulin metabolism is less likely to be affected by dietary long chain carbohydrates.

The association between fat intake and MCI has been established by a series of human and rodent studies. A randomly controlled clinical trial has shown that attention, speed and mood were impaired in a cohort of young males (aged 22±1 years) in high-fat, low-carbohydrate diets for 5 days [16], suggesting that a high-fat diet was potentially detrimental to the brain in healthy subjects. Edwards *et al.* has demonstrated that consumption of high-fat diet also led to increased simple reaction time and decreased power of attention [17]. In animal studies, rats fed with long-term high-fat diet developed hippocampal microvascular insulin resistance and significantly declined cognitive function in both of the two-trial spontaneous alternation behavior test and the novel object recognition test [18]. In addition, high fat diet (40% energy from fat) has been shown to induce biochemical changes (increased amyloid beta deposition and neurofibrillary tangle formation) and decreased synaptic plasticity in the brain of mice [18, 19].

As suggested by the human and animal studies, the association of high fat intake with MCI may be caused by insulin resistance (IR). High fat diet (HFD) is a well-established approach to induce IR in peripheral organs and hypothalamus [19, 20]. Accumulating evidence has shown that HFD caused increased circulating glucose and free fatty acid (FFA) concentrations [21], therefore led to insulin insensitivity. To our knowledge, the relationship between cognitive function and insulin sensitivity or IR has been well established by plenty of studies [22-25]. Therefore, the same mechanism may account for the increased risk of MCI caused by high fat intake in the present study. In future studies, we will measure the serum triglycerides and insulin levels to validate this hypothesis.

Besides macronutrients intake, other risk factors for the development of MCI were also identified, including age, education, hyperlipidemia and total energy intake in this study. Aging has been associated with increased risk for cardiovascular diseases and Alzheimer's disease, which

is manifested by reduced cognitive function, neurodegeneration and the onset of dementia [26]. In consistence, advanced age was associated with a decline in cognitive function in the present study. Moreover, we found that hyperlipidemia significantly increased the risk of MCI (OR 2.46, $p<0.01$), as reported by other studies [27, 28]. Educational attainment is a key component of successful cognitive aging and a major protective factor for dementia [29].Consistently, we found that higher educational level was potentially a protecting factor of MCI in this study. In addition to these demographic characteristics, we also discovered that high total energy intake increased the risk of MCI. As energy intake increased for each quartile, the risk of MCI was increased by around 2 folds (Table 3). However, the increased risk was not associated with overweight and obesity, since we didn't find significant difference in BMI and the waist/hip ratio among energy intake quartiles (data not shown). Moreover, after adjusted for energy intake, the results demonstrated that high fat and protein intake increased the risk of MCI (table 4).

There were some limitations of this study. First, it was a retrospective study; therefore, recall bias in reporting of dietary nutrients cannot be excluded, especially for those with cognitive impairment. To maximally minimize the potential recall bias we used special charts and measuring rulers or cups to help in quantifying the consumed food. Second, subjects were recruited at community hospitals, thus there was a potential risk for participation bias. The higher frequencies of vascular disease risk factors (such as diabetes, hypertension and hyperlipidemia) in participants may introduce bias towards the association between dietary and cognitive function. Third, hypertension and diabetes were self-reported, which may introduce information bias. Finally, participants were recruited only from Beijing and any generalization of the results of this study to other ethnicities should be performed with cautions.

In summary, after adjusted for age, education, hyperlipidemia and total energy intake, high fat and protein intake and low carbohydrate intake increased the risk of MCI. A balanced dietary pattern consisting of optimal fat, protein and carbohydrate ratio is potentially beneficial to the maintenance of normal cognitive function in young and middle-aged people.

**Authorship**

Weiwei Ma and Rong Xiao conceived and designed the study, Yong Zhang and Bingjie Ding collected the data, Bingjie Ding and Lei Zhao performed the statistical analyses and drafted the manuscript. And Yanxia Bi helped collect and analyze the data. All authors read and approved the

final manuscript.

**Ethics declaration**

All experimental procedures were conducted in accordance with the guidelines in the Declaration of Helsinki and approved by the Ethics Committee of Capital Medical University, Beijing(No.2014SY33).

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**Conflict of Interest**

None

**Date sharing statement**

All data used to derive the outcomes presented in the study are documented in the manuscript. No additional unpublished data are available

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Table 1 MCI by different groups of characteristics

| Variables | N(%) | Means(SD) | OR(95%CI) | *P* value |
|---|---|---|---|---|
| Total | | | | |
| Sex | | | | |
| Male | 303(45.8) | | reference | |
| Female | 358(54.2) | | 1.57(0.98-2.55) | 0.068 |
| Age | | 48.5±7.3 | | |
| <45 | 213(32.2) | | reference | |
| 45~55 | 286(43.3) | | 3.69(1.75-7.78) | 0.001 |
| >55 | 162(24.5) | | 5.36(2.47-11.63) | <0.001 |
| BMI | | 26.2±3.6 | | |
| <25 | 247(37.4) | | reference | |
| 25~29.9 | 310(46.9) | | 2.33(1.32-4.12) | 0.004 |
| ≥ 30 | 104(15.7) | | 1.98(0.94-4.15) | 0.071 |
| Race/ethnicity | | | | |
| Han | 608(92.0) | | reference | |
| Other | 53(8.0) | | 0.92(0.38-2.23) | 0.856 |
| Education(years) | | | | |
| ≤ 6 | 51(7.7) | | reference | |
| 7~12 | 481(72.8) | | 0.64(0.31-1.34) | 0.238 |
| > 12 | 129(19.5) | | 0.17(0.05-0.51) | 0.002 |
| Labor intensity | | | | |
| Light | 508(76.9) | | reference | |
| Moderate | 133(20.1) | | 1.37(0.31-6.03) | 0.679 |
| Hard | 20(3.0) | | 0.81(0.17-3.96) | 0.796 |
| Aerobic exercise | | | | |
| NO | 466(70.5) | | reference | |
| YES | 195(29.5) | | 0.83(0.49-1.41) | 0.497 |
| Smoking | | | | |
| NO | 514(77.8) | | reference | |
| YES | 147(22.2) | | 1.49(0.88-2.51) | 0.137 |
| Drinking | | | | |
| NO | 455(68.9) | | reference | |
| YES | 206(31.1) | | 0.52(0.29-0.92) | 0.027 |
| Diseases history | | | | |
| Hypertension | | | | |
| NO | 497(75.2) | | reference | |
| YES | 164(24.8) | | 1.76(1.07-2.90) | 0.026 |
| Diabetes | | | | |

| | | | |
|---|---|---|---|
| NO | 466(70.5) | reference | |
| YES | 195(29.5) | 0.85(0.52-1.41) | 0.531 |
| Hyperlipidemia | | | |
| NO | 386(58.4) | reference | |
| YES | 275(41.6) | 2.80(1.73-4.55) | <0.001 |
| MCI | | | |
| NO | 581(87.9) | | |
| YES | 80(12.1) | | |

Abbreviations: CI, confidence interval; OR, odds ratio ; SD, Standard Deviation; BMI, body mass index; MCI, mild cognitive impairment

Table 2 Quartiles of % fat of total energy

| Variable | Q1 <20% N=165 | Q2 20-28% N=165 | Q3 29-35 N=165 | Q4 >35% N=165 | *P* value |
|---|---|---|---|---|---|
| | | N (%) | | | |
| Female | 95(57.6) | 88(53.3) | 93(56.4) | 82(49.4) | 0.447 |
| Diabetes | 42(25.5) | 55(33.3) | 43(26.1) | 55(33.1) | <0.001 |
| Hypertension | 41(24.8) | 32(19.4) | 44(26.7) | 47(28.3) | 0.262 |
| Hyperlipidemia | 46(27.9) | 73(44.2) | 76(46.1) | 80(48.2) | <0.001 |
| Drinking | 56(33.9) | 47(28.5) | 50(30.3) | 53(31.9) | 0.742 |
| Smoking | 34(20.6) | 32(19.4) | 38(23) | 43(25.9) | 0.198 |
| Aerobic exercise | 43(26.1) | 52(31.5) | 54(32.7) | 46(27.7) | 0.504 |
| Education(>12years) | 33(20.0) | 41(24.8) | 31(18.8) | 24(14.5) | 0.123 |
| MCI | 6(3.6) | 14(8.5) | 28(17.0) | 32(19.3) | <0.001 |
| | | Mean(SD) | | | |
| Age (year) | 47.4(6.9) | 47.5(7.3) | 49.1(7.5) | 50.2(6.9) | <0.001 |
| BMI(kg/m2) | 26.1(3.4) | 26.1(3.6) | 26.5(3.5) | 26.2(3.9) | 0.712 |
| Total energy | 1830(612) | 1815(675) | 2365(871) | 2197(735) | < 0.001 |
| Intake(% of energy) | | | | | |
| % Carbohydrate | 68(5) | 59(4) | 51(3) | 38(7) | <0.001 |
| % Protein | 16(3) | 17(3) | 17(2) | 18(4) | <0.001 |
| % Total Fat | 16(3) | 24(2) | 31(2) | 43(6) | <0.001 |
| Intake(g/d) | | | Median(Q75-Q25) | | |
| Carbohydrate | 278(170) | 252(215) | 291(141) | 200(131) | <0.001 |

| | | | | | |
|---|---|---|---|---|---|
| Protein | 62(37) | 74(40) | 97(58) | 96(51) | <0.001 |
| Fat | 28(15) | 47(24) | 76(49) | 103(63) | <0.001 |
| Fiber | 10(9.2) | 12(9.1) | 15(8.3) | 14(10.6) | <0.001 |

Abbreviations: MCI, mild cognitive impairment; SD, Standard Deviation; Q,Quartiles; BMI, body mass index;

Table 3 risk factor of MCI by Logistic Regression Analysis

| Variable | wald | OR | 95%CI | *P* |
|---|---|---|---|---|
| BMI* | 2.828 | 1.36 | 0.95-1.96 | 0.09 |
| Age* | 7.846 | 1.72 | 1.18-2.52 | 0.005 |
| Hypertension | 0.257 | 1.15 | 0.62-2.02 | 0.61 |
| Hyperlipidemia | 12.071 | 2.46 | 1.48-4.10 | 0.001 |
| Diabetes | 0.308 | 1.17 | 0.68-2.02 | 0.58 |
| Education* | 4.677 | 0.54 | 0.31-0.94 | 0.031 |
| Energy (quartiles) | 17.251 | 1.67 | 1.31-2.12 | <0.001 |

Abbreviations: CI, confidence interval; OR, odds ratio; MCI, mild cognitive impairment

*Processing as Classification variables, BMI (<25,25-29.9, ≥ 30), age(<45,45-55,>55),education(≤ 6,6-12,>12)

Table4 association of% macronutrient (carbohydrates, fat, and protein) with incident MCI

| Variable | Cutpoint(%) | Incident MCI,N(%) | OR(95%CI)[a] | *P* |
|---|---|---|---|---|
| Carbohydrate | | | | |
| Q1 | <46 | 33(20.0) | reference | |
| Q2 | 47-54 | 25(15.2) | 0.77(0.42-1.41) | 0.39 |
| Q3 | 55-63 | 15(9.1) | 0.58(0.29-1.16) | 0.12 |
| Q4 | >63 | 7(4.2) | 0.30(0.12-0.72) | 0.007 |
| Protein | | | | |
| Q1 | <14.9 | 10(6.1) | reference | |
| Q2 | 15.0-16.5 | 20(12.1) | 1.70(0.74-3.93) | 0.21 |
| Q3 | 16.6-18.5 | 23(13.9) | 2.48(1.09-5.61) | 0.03 |
| Q4 | >18.5 | 27(16.3) | 2.77(1.24-6.15) | 0.01 |
| Fat | | | | |
| Q1 | <20 | 6(3.6) | reference | |
| Q2 | 21-28 | 14(8.5) | 2.22(0.81-6.10) | 0.12 |
| Q3 | 29-35 | 28(17.0) | 3.36(1.30-8.67) | 0.01 |
| Q4 | >35 | 32(19.3) | 3.90(1.53-9.89) | 0.004 |

Abbreviations: CI, confidence interval; OR,odds ratio; MCI, mild cognitive impairment

Adjusted for age, BMI, Education, energy(Quartiles),Hyperlipidemia

**STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies***

| Section/Topic | Item # | Recommendation | Reported on page # |
|---|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | 2 |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | 2 |
| **Introduction** | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | 3 |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | 3 |
| **Methods** | | | |
| Study design | 4 | Present key elements of study design early in the paper | 3 |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 3 |
| Participants | 6 | (*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up | 4 |
| | | (*b*) For matched studies, give matching criteria and number of exposed and unexposed | 4 |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 4,5 |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | *4,5* |
| Bias | 9 | Describe any efforts to address potential sources of bias | 9 |
| Study size | 10 | Explain how the study size was arrived at | |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | 4 |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | 5,6 |
| | | (*b*) Describe any methods used to examine subgroups and interactions | 5,6 |
| | | (*c*) Explain how missing data were addressed | 5,6 |
| | | (*d*) If applicable, explain how loss to follow-up was addressed | n/a |
| | | (*e*) Describe any sensitivity analyses | 5,6 |
| **Results** | | | |

| | | | |
|---|---|---|---|
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | 3,4 |
| | | (b) Give reasons for non-participation at each stage | 3,4 |
| | | (c) Consider use of a flow diagram | |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | 6 |
| | | (b) Indicate number of participants with missing data for each variable of interest | 6 |
| | | (c) Summarise follow-up time (eg, average and total amount) | N/A |
| Outcome data | 15* | Report numbers of outcome events or summary measures over time | 6 |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | 7 |
| | | (*b*) Report category boundaries when continuous variables were categorized | 4 |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | 7 |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | 7 |
| **Discussion** | | | |
| Key results | 18 | Summarise key results with reference to study objectives | 7 |
| **Limitations** | | | |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | 9 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | 9 |
| **Other information** | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | 10 |

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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# The Association of Macronutrients Intake with Mild Cognitive Impairment in age<65 Chinese Population



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| | |

**The Association of Macronutrients Intake with Mild Cognitive Impairment in age<65 Chinese Population**

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**Abstract**

**Objective** Macronutrients are the main sources of dietary energy and high energy intake may increase the risk of cognitive impairment. The aim of this study was to explore the correlation between daily energy intake from macronutrients and cognitive function in Chinese < 65 year old.

**Design**: This is a cross section study to explore the relationships between macronutrients intake and cognitive function. The Analysis of Variance (ANOVA) and $\chi^2$ test were used to compare the demographic characteristics, lifestyle, physical and laboratory parameters and macronutrients intake among different quartiles of % fat/energy. Multivariate logistic regression was applied to identify the potential factors related to mild cognitive impairment (MCI).

**Setting:** Beijing.

**Subjects**: Young and middle-aged subjects (age<65 years) were recruited from community. The Montreal cognitive assessment (MoCA) and Mini-mental state examination (MMSE) were used to evaluate the cognitive functions of all participants. Dietary intake was estimated with a semi-quantitative food frequency questionnaire (FFQ).

**Results** Among the 661 subjects, 80 (12.1%) had MCI, while 581(87.9%) had normal cognitive function. After adjustment for age, hyperlipidemia, education and total energy intake, the results revealed that high % fat (upper quartile: adjusted odds ratio [aOR] 3.90, 95% confidence interval [CI] 1.53-9.89, *p*=0.004), and high % protein intake (upper quartile: aOR 2.77, 95% CI 1.24-6.15) were associated with increased frequency of MCI, while high % carbohydrate intake (upper quartile: aOR 0.30, 95% CI 0.12-0.72) was correlated with decreased prevalence of MCI.

**Conclusion** The results suggested that dietary pattern with high percentage of energy intake from fat and protein and low energy intake from carbohydrate might contribute to cognitive decline in Chinese population < 65 years old.

**Key words:** Dietary pattern; mild cognitive impairment; macronutrients; energy intake

**Strengths and limitations of this study**

Compared to previously published studies, this study involved a relative younger subjects (age<65).

High percentage of energy intake from fat and protein was associated with a higher prevalence of Mild cognitive impairment (MCI).

High carbohydrate intake was negatively correlated with the MCI prevalence.

No report on the breakdown of dietary fat consumption.

## Introduction

Dietary pattern and intake of nutrients have been shown to be associated with cognitive function[1, 2]. Mediterranean diet (MD), rich in vegetables, fruit, fresh fish and olive oil, has been proven to have beneficial effects on cognitive function [3, 4]. Similarly, two earlier studies of our group have demonstrated that diet rich in marine products, fruit, vegetables and vegetable juice could prevent cognitive decline in the elderly population [5, 6]. And the long-chain omega-3 fatty acids (LC-n3-FA) and polyphenols including resveratrol, curcumin and flavonoids from these diets are likely the main nutrients beneficial to cognitive function [4, 7]. A great number of previous studies have also demonstrated that adequate dietary intake of vitamins and minerals were closely associated with decreased risk of cognitive impairment [8]. However, those studies only examined the effects of different foods and micronutrients, without considering the influence of energy intake and the source of energy in the risk of developing Mild cognitive impairment (MCI). A prospective cohort study[9] found that high average energy consumption increased the risk of cognitive impairment or dementia (OR:1.62, 95% CI:1.25-2.10) after adjustment for micronutrients, vascular disease, diabetes, smoking, BP and BMI, but it did not considered the source of energy either.

The primary determinants of total caloric intake and the largest proportion of the components of any diet are the three types of macronutrients: carbohydrates, fat and protein. The balanced ratio of carbohydrates, fat and protein was the basis of healthy diets, which ensures adequate intake of all nutrients. Up to now, however, there were limited studies that investigated the association of macronutrient (carbohydrates, fat and protein) with cognitive function. Roberts[10] *et al.* has reported that relatively high caloric intake from carbohydrates might increase the risk of MCI or dementia in elderly persons. Due to the inherent differences in Western and Chinese diets, this conclusion may not apply to Chinese population. Thus, we conducted a case-control study to explore the relationship between macronutrients and energy intake and cognitive function in a cohort of Chinese<65 years in age to control the bias of aging.

## Methods

### Participants

This cross section study was conducted in three community hospitals in Beijing, during December 1, 2015 to September 30, 2016. We identified 1197 (age<65) potentially eligible

subjects out of 4360 outpatients, among whom 777 agreed to participate (64.9% response rate) in the study. Finally, 661 participants were included in the study according to the exclusion criteria: individuals with serious diseases (cancer, severe psychiatric disorders such as depression and schizophrenia, a recent history of heart or respiratory failure and chronic liver or renal failure, n=25); individuals with conditions known to affect cognitive function (a recent history of alcohol abuse, n=43; cerebral infarction, n=27; severe brain injury, n=3); individuals with Alzheimer's disease (AD)(n=0), Parkinson's disease(PD) (n=0) or long-term frequent intake of anti-depressants and other medications for neurological diseases (n=18). All experimental procedures were conducted in accordance with the guidelines in the Declaration of Helsinki and approved by the Ethics Committee of Capital Medical University, Beijing (No.2014SY33). All participants signed a written informed consent and all had the right to terminate their participation at their willing.

**Data collection and grouping**

Questionnaire including demographic characteristics and lifestyle was performed by well-trained researchers according to the same criteria through face to face interviews. The collected data by questionnaire included age, gender, education, race/ethnicity (divided into Han and other, including Manchu, Hui, Koreans, Mongols and so forth), work intensity, smoking (yes or no), drinking (yes or no), physical exercise, disease history (hypertension, diabetes, and so forth). Height and weight were measured with height and weight scales (RGZ-120-RT, Wuxi weighing apparatus factory). Waist and hip circumferences were measured by flexible rulers, and waist-to-Hip Ratio (WHR) was calculated as waist circumference (cm) / hip circumference (cm). Blood samples were collected for the measurement of lipid levels (total cholesterol and triglyceride) with an automatic biochemistry analyzer (Olympus, AU 400, Japan). Hyperlipidemia was defined as hypercholesterolemia (serum cholesterol > 5.2 mmol/L) and/or hypertriglyceridemia (serum triglyceride > 1.7 mmol/L).

Age was categorized into three ranks: <45 years old, 45~55 years old and >55 years old. Body mass index (BMI) was calculated as weight (kg) / height$^2$ (m$^2$) and subsequently divided into three groups[11, 12]: normal (18.5~24.9 kg/m$^2$), overweight (25.0~29.9 kg/m$^2$) and obese ($\geqslant$30 kg/m$^2$). Educational levels were divided into three ranks[13]: $\leq$ 6 years (illiterate and elementary school), 7~12 years (junior high school, senior high school and technical secondary school) and > 12 years (college and graduate school). Work intensity which was estimated based on profession was

categorized into three groups[14] : light (75% of time sitting or standing and 25% of time standing with activities, such as office workers, salesman and teacher), moderate (25% of time sitting or standing and 75% of time with special occupational activities, e.g. students daily activities, motor vehicle driving, metalworking and electrical installation), and heavy (40% of time sitting or standing and 60% of time with special occupational activities, e.g. weeding, weight-bearing walking, dancing, skiing, riding a bicycle, mountain climbing, logging, manual excavation, playing basketball, mountain climbing and playing football). Aerobic exercise[15] refers to physical exercise of low to high intensity, including running/jogging, climbing, jumping rope, brisk walking, swimming, kicking shuttle cock and so on.

**Dietary questionnaire**

Dietary intake was estimated by using a semi-quantitative food frequency questionnaire (FFQ)[8 16], which included a total of 34 items (whole grain, red meat, pork, beef, mutton, chicken, fish, legume and legume product, milk, eggs, fruit and vegetables, nuts, sugared beverages, cooking oil, etc.), consumption frequency (daily, weekly, monthly, yearly or never) and the quantity of each consumption. The quantity of consumed food was estimated by using food models and measuring rulers or cups. Then the intake of nutrients per day was calculated based on the China Food Composition Database [17]. Trained dietary interviewers helped all participants in completing the FFQ to make sure the accuracy of the collected data.

**Cognitive function screening for MCI**

The Montreal cognitive assessment (MoCA) and Mini-mental state examination (MMSE) were employed to evaluate the cognitive functions of participants according to the standard protocols. The total score of MoCA is 30 and the cut-off for screening MCI is 13 for illiterate individuals, 19 for individuals with 1-6 years of education, and 24 for individuals with 7 or more years of education as previously described [8]. The total score of MMSE is 30. The cut-off scores for screening MCI is as following: 19 for illiterate individuals, 22 for individuals with 1-6 years of education and 26 for individuals with 7 or more years of education. These criteria have been proven to be appropriate for screening MCI in elderly Chinese people in a large cohort-based study [18]. The screening of MCI in the present study was a combination of these two methods with the following criteria: MoCA $\leq$ 13 and MMSE $\geq$ 20 for illiteracy; MoCA $\leq$ 19 and MMSE $\geq$ 23

for subjects with 1-6 years of education; MoCA ≤ 24 and MMSE ≥ 27 for subjects with ≥ 7 years of education.

**Statistical analysis**

Statistical analyses were performed using the SPSS 17.0 software (SPSS Inc., Chicago, IL, USA). Data was tested for normality distribution by visual inspection of histograms and the Shapiro-Wilk W-test. Continuous variables were presented as mean ± standard deviation (SD) or Median (Q), and categorical variables were described as frequencies (percentage). Logistic regression analysis was used to compare the demographic characteristics, lifestyle and physical and laboratory parameters between subjects with and without MCI. The Analysis of Variance (ANOVA) and rank sum test for continuous variables and Cochran-Mantel-Haenszel $\chi^2$ test for categorical variables were used to compare the demographic characteristics, lifestyle, physical and laboratory parameters and macronutrients intake among different quartiles of % fat/energy (percentage of energy from total fat). Multivariate logistic regression was used to identify the potential risk factors of MCI and to estimate the risk of MCI between different quartiles of % nutrients/energy (percentage of energy from each nutrient). All statistical analyses were performed with a two-tailed alpha level of 0.05.

**Results**

**Subjects**

A total of 661 subjects were included in this study. The demographic characteristics, lifestyle, physical and laboratory parameters and their association with MCI were presented in Table 1. Of all the subjects, 303 (45.8%) were males and 358 (54.2%) were females; the average age was 48.5 ± 7.3 years (30~64 years); the average BMI was 26.2 ± 3.6 kg/m$^2$; the overweight and obese group was 310 (46.9%) and 104 (15.7%), respectively; 80(12.1%) subjects had MCI and the other 581 participants (87.9%) had normal cognitive function. Greater age and BMI, and the presence of hypertension and hyperlipidemia were associated with greater prevalence of MCI, while educational level was negatively correlated with the prevalence of MCI. However, gender, race/ethnicity, labor intensity, aerobic exercise, smoking, drinking and diabetic and hypertension status were not associated with the prevalence of MCI (Table1).

Table1 end of paper

We next compared the demographic characteristics, lifestyle, physical and laboratory parameters and energy intake from each macronutrient across quartiles of % fat/energy (percentage of energy from total fat). As shown in table 2, subjects in higher % fat/energy quartiles had increased frequency of MCI, diabetes and hyperlipidemia and more advanced age. Lifestyle (smoking, drinking and exercise) and BMI were not significantly different across quartiles of % fat/energy. The total energy intake in the highest % fat/energy quartile was higher than that in the lowest quartile, but lower than that in the third % fat/energy quartile. Intake of protein and dietary fiber (in term of g/day or % of total energy) was increased across increasing % fat/energy quartiles, while the intake of carbohydrates was decreased as quartiles of % fat/energy raised. These data suggested that the increased dietary intake of fat might be associated the development of MCI.

Table 2 end of paper

Before the analysis of the relationship between macronutrients intake and cognitive function, a multivariate logistic regression analysis was employed to identify the association of BMI, age, education, hypertension, hyperlipidemia, diabetes and energy intake with MCI. In this assay, MCI status was defined as the dependent variable, while BMI, age, education, hypertension, hyperlipidemia, diabetes and energy intake were set as the independent variables. As shown in table 3, age (OR 1.72, 95% CI 1.18-2.52), hyperlipidemia (OR 2.46, 95% CI 1.48-4.10) and total energy intake (OR 1.67, 95% CI 1.31-2.12) were positively associated with the risk for MCI, while education (OR 0.54, 95% CI 0.31-0.94) was a protective factor for MCI. Although BMI was not statistically associated with the risk for MCI, a trend of increased risk of MCI was observed in subjects with higher BMI (OR 1.36, 95% CI 0.95-1.96).

Table 3 end of paper

We then explored the association of % of energy from a specific macronutrient (carbohydrates, fat and protein) with the prevalence of MCI, with adjustment for age, BMI, education, energy (quartiles) and hyperlipidemia. The risk of MCI was reduced by about 70% in the highest quartile of % carbohydrate/energy group. On the contrary, the risk for MCI was increased by nearly 2.48 and 2.77 folds in the third and the highest quartile of % protein/energy, respectively. In consistence, it was elevated by around 3.36 and 3.90 folds in the third and the highest quartile of % fat/energy, respectively (Table 4).

Table 4 end of paper

**Discussion**

In this study involving young and middle-aged population, high % fat/energy and % protein/energy intakes were associated with the increased prevalence of MCI. In contrast, high % carbohydrate/energy intake was correlated with a reduced risk of MCI. These findings suggested that a dietary pattern of high fat and protein intake and low carbohydrate intake might have adverse effects on the development of MCI. Therefore, a balanced dietary pattern that consists of optimal fat, protein and carbohydrate proportions may be beneficial to maintaining normal cognitive function in this population.

Our findings were in opposite to the results of a study by Robert *et al.*, which reported that dietary with relatively high caloric intake from carbohydrates and low caloric intake from fat and proteins might increase the risk of MCI [10]. This inconsistency may stem from the difference in the age of subjects and the source of carbohydrate in their diets. In the present study, the participants were relatively younger than the subjects in the study by Robert *et al.* (< 65 years VS 70-89 years). In addition, Chinese diets are rich in starchy foods (e.g., refined grain, tubers and their products), which represent the main source of dietary energy, while carbohydrates in Robert *et al.* study were mainly derived from simple sugars. As we known, in elderly persons, a dietary pattern high in simple sugars may disrupt glucose and insulin metabolism [19-22]. Glucose and insulin metabolism has been shown to have a close relationship with cognitive functions [23]. Therefore, we hypothesized that in Robert *et al.* study high level of simple sugar intake was a potential risk factor of MCI in the elders (median age = 79.5 years). In our study, the participants were much younger (48.5 ± 7.3 years) and obtained carbohydrates mainly from starchy foods, thus their risk of abnormal blood glucose level and insulin metabolism was smaller and they consequently had a lower prevalence of MCI. Given that, in younger population, we speculated that intake of high fat instead of high carbohydrates might represent a key dietary factor for increased risk of MCI.

The association between fat intake and MCI has been established by a series of human and rodent studies. A randomly controlled clinical trial has shown that attention, speed and mood were impaired in a cohort of young males (aged 22±1 years) in high-fat, low-carbohydrate diets for 5 days [24], suggesting that a high-fat diet was potentially detrimental to the brain in healthy subjects. Edwards *et al.* has demonstrated that consumption of high-fat diet also led to increased simple

reaction time and decreased power of attention [25]. In animal studies, rats fed with long-term high-fat diet developed hippocampal microvascular insulin resistance and significantly declined cognitive function in the two-trial spontaneous alternation behavior test and the novel object recognition test [26]. In addition, high fat diet (40% energy from fat) has been shown to induce biochemical changes (increased amyloid beta deposition and neurofibrillary tangle formation) and decreased synaptic plasticity in the brain of mice [26, 27].

As suggested by the human and animal studies, the association of high fat intake with MCI may be caused by insulin resistance (IR). High fat diet is a well-established approach to induce IR in peripheral organs and hypothalamus [27, 28]. Accumulating evidence has shown that high fat diet could cause increased blood glucose and free fatty acid (FFA) concentrations [29], therefore led to insulin insensitivity. To our knowledge, the relationship between cognitive function and insulin sensitivity or IR has been well established by plenty of studies [30-33]. Therefore, the same mechanism might account for the increased risk of MCI caused by high fat intake in the present study. We also found that hyperlipidemia (hypercholesterolemia and/or hypertriglyceridemia) was associated with the risk for MCI. But the relationship among hyperlipidemia, increased fat intake and cognitive impairment is still unclear. A systematic review and meta-analysis[34] has revealed that the reduction in triglyceride levels was more distinct in the high-fat diet groups. Holloway *et al.*[24] found no significant difference in cholesterol concentrations between high-fat diet and standard diet groups. Thus hyperlipidemia was not necessarily a result of high fat intake, and it may be independent of the high-fat diet-induced risk of MCI.

It was interesting that the prevalence of MCI was higher as the protein intake was increased (table 4). In china, the intake of dietary protein has been largely increased and the main sources of protein have been changed from vegetable proteins to animal proteins, in particular the red meats [35]. We found that when protein accounts for 15.0%-16.5% of total energy, the protein intake had no significant association with the incidence of MCI; this suggested that an appropriate protein intake is critical for maintaining normal cognitive function and that over-consumption of protein might be harmful to cognition. However, the appropriate protein intake for optimal cognitive function and for delaying the decline in cognition with advanced age remained unknown [36].

In addition to macronutrients intake, some other potential risk factors for the development of MCI were also identified in this study, including age, education, hyperlipidemia and total energy intake. Aging has been associated with increased risk for cardiovascular diseases and Alzheimer's disease, which is manifested by reduced cognitive function, neurodegeneration and the onset of dementia [37]. In consistence, advanced age was associated with a decline in cognitive function in the present study. Moreover, we found that hyperlipidemia was associated with significantly increased risk of MCI (OR 2.46, $p<0.01$), as reported by other studies [38, 39]. Educational attainment is a key component of successful maintenance of cognitive function in old people and a major protective factor for dementia [40]. Consistently, we found that higher educational level was potentially a protective factor against MCI in this study. In addition to these demographic characteristics, we also discovered that high total energy intake was correlated with increased risk of MCI. As energy intake increased for each quartile, the risk of MCI was increased by around 1.66 folds (Table 3). However, the increased risk was not associated with overweight and obesity, since we didn't find significant difference in BMI and WHR among energy intake quartiles. Moreover, after adjusted for energy intake, the results demonstrated that high fat and protein intake was associated with increased risk of MCI (table 4).

There were some limitations of this study. First, recall bias in reporting of dietary nutrients cannot be excluded, especially for those with cognitive impairment. To maximally minimize the potential recall bias we used special model and measuring rulers or cups to help in quantifying the consumed food. Second, the subjects were recruited at community hospitals, thus there was a potential risk for participation bias. The higher frequencies of vascular disease risk factors (such as diabetes, hypertension and hyperlipidemia) in participants might introduce bias towards the association between dietary nutrients intake and cognitive function. Third, hypertension and diabetes were self-reported, which might introduce information bias. Finally, the participants were recruited only from Beijing and any generalization of the results of this study to other locations and to other ethnicities should be performed with cautions.

In summary, after adjusted for age, education, hyperlipidemia and total energy intake, high fat and protein intake and low carbohydrate intake were associated with greater risk for MCI. A balanced dietary pattern consisting of optimal fat, protein and carbohydrate ratio is potentially beneficial to the maintenance of normal cognitive function in young and middle-aged people.

**Authorship**

Weiwei Ma and Rong Xiao conceived and designed the study, Yong Zhang and Bingjie Ding collected the data, Bingjie Ding performed the statistical analyses and drafted the manuscript, Lei Zhao drafted and revised the manuscript, and Yanxia Bi helped to collect and analyze the data. All authors read and approved the final manuscript.

**Ethics declaration**

All experimental procedures were conducted in accordance with the guidelines in the Declaration of Helsinki and approved by the Ethics Committee of Capital Medical University, Beijing (No.2014SY33).

**Financial Support**

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**Data sharing statement**

The materials and datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

**Conflict of Interest**

None

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Table 1 MCI by different groups of characteristics

| Variables | N(%) | Means(SD) | OR(95%CI) | *P* value |
|---|---|---|---|---|
| Total | | | | |
| Sex | | | | |
| Male | 303(45.8) | | reference | |
| Female | 358(54.2) | | 1.57(0.98-2.55) | 0.068 |
| Age(years) | | 48.5±7.3 | | |
| <45 | 213(32.2) | | reference | |
| 45~55 | 286(43.3) | | 3.69(1.75-7.78) | 0.001 |
| >55 | 162(24.5) | | 5.36(2.47-11.63) | <0.001 |
| BMI(kg/m$^2$) | | 26.2±3.6 | | |
| <25 | 247(37.4) | | reference | |
| 25~29.9 | 310(46.9) | | 2.33(1.32-4.12) | 0.004 |
| ≥ 30 | 104(15.7) | | 1.98(0.94-4.15) | 0.071 |
| WHR | | | | |
| Normal | 261(39.5) | | reference | |
| Abnormal* | 400(60.5) | | 1.04(0.64-1.67) | 0.886 |
| Race/ethnicity | | | | |
| Han | 608(92.0) | | reference | |
| Other | 53(8.0) | | 0.92(0.38-2.23) | 0.856 |
| Education(years) | | | | |
| ≤ 6 | 51(7.7) | | reference | |
| 7~12 | 481(72.8) | | 0.64(0.31-1.34) | 0.238 |
| > 12 | 129(19.5) | | 0.17(0.05-0.51) | 0.002 |
| Labor intensity | | | | |
| Light | 508(76.9) | | reference | |
| Moderate | 133(20.1) | | 1.37(0.31-6.03) | 0.679 |
| Hard | 20(3.0) | | 0.81(0.17-3.96) | 0.796 |
| Aerobic exercise | | | | |
| NO | 466(70.5) | | reference | |
| YES | 195(29.5) | | 0.83(0.49-1.41) | 0.497 |
| Smoking | | | | |
| NO | 514(77.8) | | reference | |
| YES | 147(22.2) | | 1.49(0.88-2.51) | 0.137 |
| Drinking | | | | |
| NO | 455(68.9) | | reference | |
| YES | 206(31.1) | | 0.52(0.29-0.92) | 0.027 |
| Diseases history | | | | |
| Hypertension | | | | |
| NO | 497(75.2) | | reference | |
| YES | 164(24.8) | | 1.76(1.07-2.90) | 0.026 |

| | | | |
|---|---|---|---|
| Diabetes | | | |
| NO | 466(70.5) | reference | |
| YES | 195(29.5) | 0.85(0.52-1.41) | 0.531 |
| Hyperlipidemia | | | |
| NO | 386(58.4) | reference | |
| YES | 275(41.6) | 2.80(1.73-4.55) | <0.001 |
| MCI | | | |
| NO | 581(87.9) | | |
| YES | 80(12.1) | | |

Abbreviations: CI, confidence interval; OR, odds ratio ; SD, Standard Deviation; BMI, body mass index; WHR, waist-to-hip ratio, MCI, mild cognitive impairment
*WHR >0.8 for female, WHR>0.9 for male.

Table 2 Characteristics of subjects by % fat intake

| Variable | Quartiles of % fat of total energy | | | | *P* value |
|---|---|---|---|---|---|
| | Q1 <20% N=165 | Q2 20-28% N=165 | Q3 29-35 N=165 | Q4 >35% N=165 | |
| | N (%) | | | | |
| Female | 95(57.6) | 88(53.3) | 93(56.4) | 82(49.4) | 0.447 |
| Diabetes | 42(25.5) | 55(33.3) | 43(26.1) | 55(33.1) | <0.001 |
| Hypertension | 41(24.8) | 32(19.4) | 44(26.7) | 47(28.3) | 0.262 |
| Hyperlipidemia | 46(27.9) | 73(44.2) | 76(46.1) | 80(48.2) | <0.001 |
| Drinking | 56(33.9) | 47(28.5) | 50(30.3) | 53(31.9) | 0.742 |
| Smoking | 34(20.6) | 32(19.4) | 38(23) | 43(25.9) | 0.198 |
| Aerobic exercise | 43(26.1) | 52(31.5) | 54(32.7) | 46(27.7) | 0.504 |
| Education(>12years) | 33(20.0) | 41(24.8) | 31(18.8) | 24(14.5) | 0.123 |
| MCI | 6(3.6) | 14(8.5) | 28(17.0) | 32(19.3) | <0.001 |
| | Mean(SD) | | | | |
| Age (year) | 47.4(6.9) | 47.5(7.3) | 49.1(7.5) | 50.2(6.9) | <0.001 |
| BMI(kg/m2) | 26.1(3.4) | 26.1(3.6) | 26.5(3.5) | 26.2(3.9) | 0.712 |
| WHR | 0.89(0.08) | 0.89(0.08) | 0.89(0.07) | 0.89(0.06) | 0.903 |
| Total energy | 1830612) | 1815(675) | 2365(871) | 2197(735) | <0.001 |
| Intake(% of energy) | | | | | |
| % Carbohydrate | 68(5) | 59(4) | 51(3) | 38(7) | <0.001 |
| % Protein | 16(3) | 17(3) | 17(2) | 18(4) | <0.001 |
| | | | | | |
| Intake(g/d) | | Median(Q75-Q25) | | | |
| Carbohydrate | 278(170) | 252(215) | 291(141) | 200(131) | <0.001 |
| Protein | 62(37) | 74(40) | 97(58) | 96(51) | <0.001 |
| Fat | 28(15) | 47(24) | 76(49) | 103(63) | <0.001 |
| Fiber | 10(9.2) | 12(9.1) | 15(8.3) | 14(10.6) | <0.001 |

Abbreviations: MCI, mild cognitive impairment; SD, Standard Deviation; Q,

Quartiles; BMI, body mass index; WHR, waist-to-hip ratio

Table 3 Risk factor of MCI by Logistic Regression Analysis

| Variable | wald | OR | 95%CI | *P* |
|---|---|---|---|---|
| BMI* | 2.828 | 1.36 | 0.95-1.96 | 0.09 |
| Age* | 7.846 | 1.72 | 1.18-2.52 | 0.005 |
| Hypertension | 0.257 | 1.15 | 0.62-2.02 | 0.61 |
| Hyperlipidemia | 12.071 | 2.46 | 1.48-4.10 | 0.001 |
| Diabetes | 0.308 | 1.17 | 0.68-2.02 | 0.58 |
| Education* | 4.677 | 0.54 | 0.31-0.94 | 0.031 |
| Energy (quartiles) | 17.251 | 1.67 | 1.31-2.12 | <0.001 |

Abbreviations: CI, confidence interval; OR, odds ratio; MCI, mild cognitive impairment; BMI, body mass index.

*Processing as Classification variables, BMI (<25,25-29.9, ≥ 30), age(<45,45-55,>55),education(≤ 6,6-12,>12)

Table 4 Association of % macronutrients (carbohydrates, fat, and protein) with incidence of MCI

| Variable | Cutpoint(%) | Incident MCI,N(%) | OR(95%CI)[a] | *P* |
|---|---|---|---|---|
| Carbohydrate | | | | |
| Q1 | <46 | 33(20.0) | reference | |
| Q2 | 47-54 | 25(15.2) | 0.77(0.42-1.41) | 0.39 |
| Q3 | 55-63 | 15(9.1) | 0.58(0.29-1.16) | 0.12 |
| Q4 | >63 | 7(4.2) | 0.30(0.12-0.72) | 0.007 |
| Protein | | | | |
| Q1 | <14.9 | 10(6.1) | reference | |
| Q2 | 15.0-16.5 | 20(12.1) | 1.70(0.74-3.93) | 0.21 |
| Q3 | 16.6-18.5 | 23(13.9) | 2.48(1.09-5.61) | 0.03 |
| Q4 | >18.5 | 27(16.3) | 2.77(1.24-6.15) | 0.01 |
| Fat | | | | |
| Q1 | <20 | 6(3.6) | reference | |
| Q2 | 21-28 | 14(8.5) | 2.22(0.81-6.10) | 0.12 |
| Q3 | 29-35 | 28(17.0) | 3.36(1.30-8.67) | 0.01 |
| Q4 | >35 | 32(19.3) | 3.90(1.53-9.89) | 0.004 |

Abbreviations: CI, confidence interval; OR,odds ratio; MCI, mild cognitive impairment

Adjusted for age, BMI, Education, energy(Quartiles),Hyperlipidemia

**STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies***

| Section/Topic | Item # | Recommendation | Reported on page # |
|---|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | 2 |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | 2 |
| **Introduction** | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | 3 |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | 3 |
| **Methods** | | | |
| Study design | 4 | Present key elements of study design early in the paper | 3 |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 3,4 |
| Participants | 6 | (*a*) Give the eligibility criteria, and the sources and methods of selection of participants | 4 |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 4,5 |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | 4,5 |
| Bias | 9 | Describe any efforts to address potential sources of bias | *10* |
| Study size | 10 | Explain how the study size was arrived at | 3 |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | 4,5 |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | 6 |
| | | (*b*) Describe any methods used to examine subgroups and interactions | 6 |
| | | (*c*) Explain how missing data were addressed | N/A |
| | | (*d*) If applicable, describe analytical methods taking account of sampling strategy | 6 |
| | | (*e*) Describe any sensitivity analyses | N/A |
| **Results** | | | |

| | | | |
|---|---|---|---|
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | 3 |
| | | (b) Give reasons for non-participation at each stage | 3 |
| | | (c) Consider use of a flow diagram | |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | 6 |
| | | (b) Indicate number of participants with missing data for each variable of interest | N/A |
| Outcome data | 15* | Report numbers of outcome events or summary measures | 6 |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | 6，7 |
| | | (*b*) Report category boundaries when continuous variables were categorized | 6.7 |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | 6.7 |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | N／A |
| **Discussion** | | | |
| Key results | 18 | Summarise key results with reference to study objectives | 8 |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | 10 |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | 10 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | 10 |
| **Other information** | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | 11 |

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

# The association between macronutrients intakes and cognition in individuals aged <65 in China: A cross sectional study

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| | |

**The association between macronutrients intakes and cognition in individuals aged <65 in China: A cross sectional study**

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**Abstract**

**Objective** The aim of this retrospective study was to explore the correlation between daily energy intake from macronutrients and cognitive functions in Chinese population aged less than 65 years.

**Design**: This is a cross sectional study to explore the relationships between macronutrients intake and cognitive function. The Analysis of Variance (ANOVA) and $\chi^2$ test were used to compare the demographic and physical characteristics, lifestyle, and laboratory parameters with the intake of macronutrients among different quartiles of % fat/energy. Multivariate logistic regression analysis was applied to identify the potential risk factors of mild cognitive impairment (MCI).

**Subjects**: Young and middle-aged subjects (age<65 years) were recruited from Beijing, China. The Montreal cognitive assessment (MoCA) and Mini-mental state examination (MMSE) were used to evaluate the cognitive functions, and the dietary intake of the subjects was estimated with a semi-quantitative food frequency questionnaire (FFQ).

**Results:** Among the 661 subjects, 80 (12.1%) had MCI, while 581(87.9%) had normal cognitive functions. On evaluating the data based on age group, educational background, and conditions of hyperlipidemia and total energy intake, the results revealed that high % fat (upper quartile: adjusted odds ratio [aOR] 3.90, 95% confidence interval [CI] 1.53-9.89, *p*=0.004), and high % protein intake (upper quartile: aOR 2.77, 95% CI 1.24-6.15) were greatly associated with increased frequency of MCI, while high % carbohydrate intake (upper quartile: aOR 0.30, 95% CI 0.12-0.72) was correlated with decreased prevalence of MCI.

**Conclusion:** The dietary pattern with high percentage of energy intake from fat and protein, and low energy intake from carbohydrate might have association with cognitive decline in Chinese population < 65 years old.

**Key words:** Dietary pattern; mild cognitive impairment; macronutrients; energy intake

**Strengths and limitations of this study**

1. Compared to previously published studies, this study involved relatively younger subjects (age<65).
2. High percentage of energy intake from fat and protein was associated with a higher prevalence of Mild cognitive impairment (MCI).
3. High carbohydrate intake was negatively correlated with the MCI prevalence.
4. There was no report on the breakdown of dietary fat consumption.

## Introduction

Macronutrients including fat, protein and carbohydrate are the main sources of dietary energy, and high-energy intake may increase the risk of cognitive impairment. Dietary pattern and intake of nutrients have been shown to be associated with cognitive functions[1, 2]. Mediterranean diet (MD), rich in fresh vegetables, fruits, fish and olive oil, has been reported to have associations with declined cognitive functions [3, 4]. Similarly, two earlier studies of our research group have previously demonstrated that diet rich in marine products, fruits, vegetables and vegetable juice could prevent cognitive decline in the elderly population [5, 6]. Moreover, it was demonstrated that the long-chain omega-3 fatty acids (LC-n3-FA) and polyphenols including resveratrol, curcumin and flavonoids from these diets are likely the main nutrients beneficial to cognitive function [4, 7]. Some previous study has reported that adequate dietary intake of vitamins and minerals were closely associated with decreased risk of cognitive impairment [8]. However, those studies could examine only the cumulative effects of different foods and micronutrients, without considering the influence of energy intake and the source of energy as a possible risk factor in developing Mild cognitive impairment (MCI). A prospective cohort study[9] reported that the high average energy consumption could increase the risk of cognitive impairment or dementia (OR:1.62, 95% CI:1.25-2.10), after analyzing the factors like micronutrients, vascular disease, diabetes, smoking, BP and BMI, but this study include the differential sources of energy intake.

The primary determinants of total caloric intake and the largest proportion of the components of any diet include the three types of macronutrients: carbohydrates, fat and protein. The balanced ratio of carbohydrates, fat and protein was the basis of healthy diets, which ensures adequate intake of all nutrients. Up to now, however, there were limited studies that investigated the significant affect of macronutrient (carbohydrates, fat and protein) with cognitive function. Roberts *et al.* [10] has reported that a relatively high caloric intake from carbohydrates might increase the risk of MCI or dementia in elderly persons. Due to the inherent differences in Western and Chinese diets, this conclusion may not significantly apply to Chinese population. Thus, we conducted a case-control study to explore the relationship between macronutrients and energy intake and cognitive functions in a cohort of Chinese population less than 65 years of age to control the bias of aging.

## Methods

**Subjects**

This retrospective study was conducted in three community hospitals in Beijing, during December 1, 2015 to September 30, 2016. We identified 1197 (age<65) potentially eligible subjects out of 4360 outpatients, and 777 among them agreed to participate (64.9% response rate) in the study. Finally, 661 participants were included in the study according to the exclusion criteria: individuals with serious diseases (cancer, severe psychiatric disorders such as depression and schizophrenia, a recent history of heart or respiratory failure and chronic liver or renal failure, n=25); individuals with conditions known to affect cognitive functions (a recent history of alcohol abuse, n=43; cerebral infarction, n=27; severe brain injury, n=3); individuals with Alzheimer's disease (AD) (n=0), Parkinson's disease (PD) (n=0) or long-term frequent intake of anti-depressants and other medications for neurological diseases (n=18). All experimental procedures were conducted in accordance with the guidelines in the Declaration of Helsinki and approved by the Ethics Committee of Capital Medical University, Beijing (No.2014SY33). All participants signed a written informed consent and had the right to terminate their participation at their willing.

**Data collection and grouping**

Questionnaire including demographic characteristics and lifestyle was prepared and the data was collected and assessed by well-trained researchers by conducting face-to-face interviews. The collected data by questionnaire included age, gender, education, race/ethnicity (divided into Han and other, including Manchu, Hui, Koreans, Mongols and so forth), work intensity, smoking (yes or no), drinking (yes or no), physical exercise, and disease history (hypertension, diabetes, and so forth). Height and weight were measured with height and weight scales (RGZ-120-RT, Wuxi weighing apparatus factory). Waist and hip circumferences were measured by flexible rulers, and Waist-to-Hip Ratio (WHR) was calculated as waist circumference (cm) / hip circumference (cm). Blood samples were collected for quantifying the lipid levels (total cholesterol and triglyceride) with an auto-analyzer (Olympus, AU 400, Japan). Hyperlipidemia was defined as hypercholesterolemia (serum cholesterol > 5.2 mmol/L) and/or hypertriglyceridemia (serum triglyceride > 1.7 mmol/L).

Age was categorized into three groups: <45 years old, 45~55 years old and >55 years old. Body mass index (BMI) was calculated as weight (kg) / height$^2$ (m$^2$) and subsequently divided into three

groups[11, 12]: normal (18.5~24.9 kg/m$^2$), overweight (25.0~29.9 kg/m$^2$) and obese (⩾30 kg/m$^2$). Educational levels were divided into three ranks[13]: ≤ 6 years (illiterate and elementary school), 7~12 years (junior high school, senior high school and technical secondary school) and > 12 years (college and graduate school). Work intensity which was estimated based on their profession was categorized into three groups[14]: light (75% of time sitting or standing and 25% of time standing with activities, such as office workers, salesman and teacher), moderate (25% of time sitting or standing and 75% of time with special occupational activities, e.g. students daily activities, motor vehicle driving, metalworking and electrical installation), and heavy (40% of time sitting or standing and 60% of time with special occupational activities, e.g. weeding, weight-bearing walking, dancing, skiing, riding a bicycle, mountain climbing, logging, manual excavation, playing basketball and football). Aerobic exercise[15] refers to physical exercise of low to high intensity, including running/jogging, climbing, jumping rope, brisk walking, swimming and playing badminton.

**Dietary questionnaire**

Dietary intake was estimated by using a semi-quantitative food frequency questionnaire (FFQ)[8 16], which included a total of 34 items (whole grain, red meat, pork, beef, mutton, chicken, fish, legume and legume product, milk, eggs, fruits and vegetables, nuts, sugared beverages, cooking oil, etc.), consumption frequency (daily, weekly, monthly, yearly or never) and the quantity of each item consumed. The quantity of food consumed was estimated using food models and measuring rulers or cups. Subsequently, the intake of nutrients per day was calculated based on the China Food Composition Database[17]. Trained dietary interviewers helped all participants in completing the FFQ to make sure the accuracy of the collected data.

**Cognitive function screening for MCI**

The Montreal cognitive assessment (MoCA) and Mini-mental state examination (MMSE) were employed to evaluate the cognitive functions of participants according to the standard protocols. The total scores of MoCA was 30 and the cut-off for screening MCI was 13 for illiterate individuals, 19 for individuals with 1-6 years of education, and 24 for individuals with 7 or more years of education as previously described[8]. The total scores of MMSE was 30, and the cut-off scores for screening MCI were as follows: 19 for illiterate individuals, 22 for individuals with 1-6

years of education and 26 for individuals with 7 or more years of education. These criteria we followed have been proven to be appropriate for screening MCI in elderly Chinese people in a large cohort-based study [18]. The screening of MCI in the present study was a combination of these two methods with the following criteria: MoCA ≤ 13 and MMSE ≥ 20 for illiteracy; MoCA ≤ 19 and MMSE ≥ 23 for subjects with 1-6 years of education; MoCA ≤ 24 and MMSE ≥ 27 for subjects with ≥ 7 years of education.

**Statistical analysis**

Statistical analyses were performed using the SPSS 17.0 software (SPSS Inc., Chicago, IL, USA). Data was tested for normality distribution by visual inspection of histograms and the Shapiro-Wilk W-test. Continuous variables were presented as mean ± standard deviation (SD) or Median (Q), and categorical variables were described as frequencies (percentage). Logistic regression analysis was used to compare the demographic characteristics, lifestyle and physical and laboratory parameters between subjects with and without MCI. The Analysis of Variance (ANOVA) and rank sum test for continuous variables and Cochran-Mantel-Haenszel $\chi^2$ test for categorical variables were used to compare the demographic characteristics, lifestyle, physical and laboratory parameters and macronutrients intake among different quartiles of % fat/energy (percentage of energy from total fat). Multivariate logistic regression was used to identify the potential risk factors of MCI and to estimate the risk of MCI between different quartiles of % nutrients/energy (percentage of energy from each nutrient). All statistical analyses were performed with a two-tailed alpha level of 0.05.

**Results**

**Demographic and physical characteristics of subjects**

A total of 661 subjects were included in this study. The demographic and physical characteristics, lifestyle, and laboratory parameters and their association with MCI were presented in Table 1. Of all the subjects, 303 (45.8%) were males and 358 (54.2%) were females; the average age was 48.5 ± 7.3 years (30~64 years); the average BMI was 26.2 ± 3.6 kg/m$^2$; the overweight and obese group included 310 (46.9%) and 104 (15.7%), respectively; 80(12.1%) subjects had MCI and the other 581 participants (87.9%) had normal cognitive functions. Increased age and BMI, and the presence of hypertension and hyperlipidemia were associated with

greater prevalence of MCI, while educational level was negatively correlated with the prevalence of MCI. However, other factors such as gender, race/ethnicity, labor intensity, aerobic exercise, smoking, drinking, diabetic and hypertension status were not associated with the prevalence of MCI (Table 1).

We next compared the demographic characteristics, lifestyle, physical and laboratory parameters and energy intake from each macronutrient across quartiles of % fat/energy (percentage of energy from total fat). As shown in table 2, subjects in higher % fat/energy quartiles had shown increased frequency of MCI, with diabetes and hyperlipidemia at more advanced age. Lifestyle (smoking, drinking and exercise) and BMI were not significantly different across quartiles of % fat/energy. The total energy intake in the highest % fat/energy quartile was higher than that in the lowest quartile, but lower than that in the third % fat/energy quartile. Intake of protein and dietary fiber (in term of g/day or % of total energy) was increased across increasing % fat/energy quartiles, while the intake of carbohydrates was decreased as quartiles of % fat/energy raised. These data suggested that the increased dietary intake of fat might be associated with the development of MCI.

Before analysis of the relationship between macronutrients intake and cognitive function, a multivariate logistic regression analysis was employed to identify the association of BMI, age, education, hypertension, hyperlipidemia, diabetes and energy intake with MCI. In this assay, MCI status was defined as the dependent variable, while BMI, age, education, hypertension, hyperlipidemia, diabetes and energy intake were set as the independent variables. As shown in table 3, age (OR 1.72, 95% CI 1.18-2.52), hyperlipidemia (OR 2.46, 95% CI 1.48-4.10) and total energy intake (OR 1.67, 95% CI 1.31-2.12) were positively associated with the risk for MCI, while education (OR 0.54, 95% CI 0.31-0.94) was a protective factor for MCI. Although BMI was not significantly associated with the risk for MCI, a trend exhibiting increased risk of MCI was observed in subjects with higher BMI (OR 1.36, 95% CI 0.95-1.96).

We then explored the association of % of energy from a specific macronutrient (carbohydrates, fat and protein) on the prevalence of MCI, with their age, BMI, education, energy (quartiles) and

hyperlipidemia. The risk of MCI was reduced by about 70% in the highest quartile of % carbohydrate/energy group. On the contrary, the risk for MCI was increased to nearly 2.48 and 2.77 fold in the third and the highest quartile of % protein/energy, respectively. In consistence, the risk for MCI was elevated to around 3.36 and 3.90 fold in the third and the highest quartile of % fat/energy, respectively (Table 4).

**Discussion**

In this study involving young and middle-aged population, a higher % fat/energy and % protein/energy intakes were associated with an increased prevalence of MCI. In contrast, high % carbohydrate/energy intake was correlated with a reduced risk of MCI. These findings suggested that a dietary pattern of high fat and protein intake and a low carbohydrate intake might have adverse effects on the development of MCI. Therefore, a balanced dietary pattern that consists of optimal fat, protein and carbohydrate proportions may be beneficial to maintain normal cognitive function in this population.

Our findings were contrary to the results of a study by Robert *et al.*, which reported that diet with a relatively high caloric intake from carbohydrates and a low caloric intake from fat and proteins might increase the risk of MCI [10]. This inconsistency may stem from the difference in the age of subjects and the differential source of carbohydrate in their diets. In the present study, the participants were relatively younger than the subjects in the study by Robert *et al.* (< 65 years VS 70-89 years). In addition, Chinese diets are rich in starchy foods (e.g., refined grain, tubers and their products), which might represent the main source of dietary energy, while carbohydrates in Robert *et al.* study were mainly derived from simple sugars. As we know,, elderly persons having a dietary pattern high in simple sugars may often disrupt the normal glucose and insulin metabolism [19-22]. Glucose and insulin metabolism has been shown to have a close relationship with cognitive functions [23]. Therefore, we hypothesized that in the study by Robert *et al.,* a high level of simple sugar intake was a potential risk factor of MCI in the elders (median age = 79.5 years). In our study, the participants were much younger (48.5 ± 7.3 years) and obtained carbohydrates mainly from starchy foods, thus their risk of abnormal blood glucose level and insulin metabolism was minimal and they consequently showed a lower prevalence of MCI. Collectively, we

speculated that intake of high fat instead of high carbohydrates might represent a key dietary factor for increased risk of MCI in younger population.

The association between fat intake and MCI has been well established by conducting a series of human and rodent studies. A randomly controlled clinical trial has shown that attention, speed and mood were impaired in a cohort of young males (aged 22±1 years) subjected to high-fat, low-carbohydrate diets for 5 days [24], suggesting that a high-fat diet was potentially detrimental to the brain in healthy subjects. Edwards *et al.* had demonstrated that consumption of a high-fat diet led to increased simple reaction time and decreased power of attention [25]. Moreover, in animal studies, rats fed with long-term high-fat diet developed hippocampal microvascular insulin resistance and significantly declined cognitive function in the two-trial spontaneous alternation behavior test and the novel object recognition test [26]. In addition, a high fat diet (40% energy from fat) had shown to induce biochemical changes (increased amyloid beta deposition and neurofibrillary tangle formation) and decreased synaptic plasticity in the brain of mice [26, 27].

As suggested by the human and animal studies, the effect of high fat intake on MCI might have resulted due to insulin resistance (IR). High fat diet is regarded as a well-established approach to induce IR in peripheral organs and hypothalamus [27, 28]. Accumulating evidence has shown that a high fat diet could cause increased blood glucose levels and free fatty acid (FFA) concentrations [29], and subsequent insulin insensitivity. However, the relationship between cognitive function and insulin sensitivity or IR has been well established by conducting many studies [30-33]. Therefore, we assumed that a similar mechanism might have accounted for the increased risk of MCI caused by high fat intake in this present study. We also found that hyperlipidemia (hypercholesterolemia and/or hypertriglyceridemia) was associated with the risk for developing MCI. But the relationship among hyperlipidemia, increased fat intake and cognitive impairment is still unclear. A systematic review and meta-analysis[34] showed that, the reduction in triglyceride levels was more distinct in the high-fat diet groups. Holloway *et al.*[24] have reported that there is no significant difference in cholesterol concentrations between high-fat diet and standard diet groups. Thus hyperlipidemia was not necessarily a result of high fat intake, and it might be independent of the high-fat diet-induced risk of MCI.

Interestingly, we have noticed that the prevalence of MCI was higher as the protein intake was increased (table 4). In china, during recent years, the intake of dietary protein among

population have increased, and the main sources of protein have changed from vegetable proteins to animal proteins, in particular the red meats [35]. We speculated that, when protein accounts for only 15.0%-16.5% of total energy, the protein intake might not show any significant association with the incidence of MCI. Moreover, it suggests that an appropriate protein intake is critical for maintaining normal cognitive functions and that over-consumption of protein might be harmful to cognition. However, the appropriate protein intake for optimal cognitive functions and to delay the decline in cognition with advanced age remained unknown [36].

In addition to macronutrients intake, we identified other potential risk factors for the development of MCI in this study, including age, education, hyperlipidemia and total energy intake. Aging has been associated with an increased risk of cardiovascular diseases and Alzheimer's disease, which is manifested by reduced cognitive function, neurodegeneration and the onset of dementia [37]. In consistence with this previous study, advanced age was associated with a decline in cognitive function in the present study. Moreover, we found that hyperlipidemia was associated with significantly increased risk of MCI (OR 2.46, $p<0.01$), as reported by other studies [38, 39]. Educational attainment is a key component of successful maintenance of cognitive function in old people, and thus serve as a major protective factor for dementia [40]. Consistently, we found that higher educational level was potentially a protective factor against MCI in this study. In addition to these demographic characteristics, we also discovered that a high total energy intake was significantly correlated with increased risk of MCI. Consequent with an energy intake increase during each quartile, the risk of MCI was increased by around 1.66 folds (Table 3). However, this increased risk was not associated with overweight and obesity, since we didn't find any significant difference in BMI and WHR among energy intake quartiles. Moreover, after adjusted for energy intake, the results demonstrated that high fat and protein intake was associated with increased risk of MCI (table 4).

There were some limitations of this study. Firstly, being a retrospective study, recall bias in reporting of dietary nutrients could not be excluded, especially for those with cognitive impairment. To maximally minimize the potential recall bias, we used special model and measuring rulers or cups to help in quantifying the consumed food. Secondly, as the subjects were recruited at community hospitals, the study exhibited a potential risk for participation bias.

Moreover, the higher frequencies of vascular disease risk factors (such as diabetes, hypertension and hyperlipidemia) in participants, might introduce bias towards the association between dietary nutrients intake and cognitive function. Thirdly, hypertension and diabetes were self-reported, which might introduce information bias. Finally, the participants were recruited only from Beijing, and any generalization of the results of this study to other locations and to other ethnicities should be performed with cautions.

In summary, after adjusted for age, education, hyperlipidemia and total energy intake, high fat and protein intake and low carbohydrate intake were associated with greater risk for MCI. A balanced dietary pattern consisting of optimal fat, protein and carbohydrate ratio may be potentially beneficial to the maintenance of normal cognitive functions in young and middle-aged people.

**Authorship**

WWM and RX conceived and designed the study, YZ and BJD collected the data, BJD performed the statistical analyses and drafted the manuscript, LZ drafted and revised the manuscript, and YXB helped in collection and analysis of the data. All authors read and approved the final manuscript.

**Ethics declaration**

All experimental procedures were conducted in accordance with the guidelines in the Declaration of Helsinki and approved by the Ethics Committee of Capital Medical University, Beijing (No.2014SY33).

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**Data sharing statement**

The materials and datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Conflict of Interest**

None

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Table 1. MCI by different groups of characteristics

| Variables | N (%) | Means (SD) | OR (95%CI) | *P* value |
|---|---|---|---|---|
| Total | | | | |
| Sex | | | | |
| Male | 303(45.8) | | reference | |
| Female | 358(54.2) | | 1.57(0.98-2.55) | 0.068 |
| Age (years) | | 48.5±7.3 | | |
| <45 | 213(32.2) | | reference | |
| 45~55 | 286(43.3) | | 3.69(1.75-7.78) | 0.001 |
| >55 | 162(24.5) | | 5.36(2.47-11.63) | <0.001 |
| BMI (kg/m$^2$) | | 26.2±3.6 | | |
| <25 | 247(37.4) | | reference | |
| 25~29.9 | 310(46.9) | | 2.33(1.32-4.12) | 0.004 |
| ≥ 30 | 104(15.7) | | 1.98(0.94-4.15) | 0.071 |
| WHR | | | | |
| Normal | 261(39.5) | | reference | |
| Abnormal* | 400(60.5) | | 1.04(0.64-1.67) | 0.886 |
| Race/ethnicity | | | | |
| Han | 608(92.0) | | reference | |
| Other | 53(8.0) | | 0.92(0.38-2.23) | 0.856 |
| Education (years) | | | | |
| ≤ 6 | 51(7.7) | | reference | |
| 7~12 | 481(72.8) | | 0.64(0.31-1.34) | 0.238 |
| > 12 | 129(19.5) | | 0.17(0.05-0.51) | 0.002 |
| Labor intensity | | | | |
| Light | 508(76.9) | | reference | |

| | | | |
|---|---|---|---|
| Moderate | 133(20.1) | 1.37(0.31-6.03) | 0.679 |
| Hard | 20(3.0) | 0.81(0.17-3.96) | 0.796 |
| Aerobic exercise | | | |
| NO | 466(70.5) | reference | |
| YES | 195(29.5) | 0.83(0.49-1.41) | 0.497 |
| Smoking | | | |
| NO | 514(77.8) | reference | |
| YES | 147(22.2) | 1.49(0.88-2.51) | 0.137 |
| Drinking | | | |
| NO | 455(68.9) | reference | |
| YES | 206(31.1) | 0.52(0.29-0.92) | 0.027 |
| Diseases history | | | |
| Hypertension | | | |
| NO | 497(75.2) | reference | |
| YES | 164(24.8) | 1.76(1.07-2.90) | 0.026 |
| Diabetes | | | |
| NO | 466(70.5) | reference | |
| YES | 195(29.5) | 0.85(0.52-1.41) | 0.531 |
| Hyperlipidemia | | | |
| NO | 386(58.4) | reference | |
| YES | 275(41.6) | 2.80(1.73-4.55) | <0.001 |
| MCI | | | |
| NO | 581(87.9) | | |
| YES | 80(12.1) | | |

Abbreviations: CI, confidence interval; OR, odds ratio ; SD, Standard Deviation; BMI, body mass index; WHR, waist-to-hip ratio, MCI, mild cognitive impairment
*WHR >0.8 for female, WHR>0.9 for male.

Table 2. Characteristics of subjects by % fat intake

| Variable | Quartiles of % fat of total energy | | | | *P* value |
|---|---|---|---|---|---|
| | Q1 <20% N=165 | Q2 20-28% N=165 | Q3 29-35 N=165 | Q4 >35% N=165 | |
| | N (%) | | | | |
| Female | 95(57.6) | 88(53.3) | 93(56.4) | 82(49.4) | 0.447 |
| Diabetes | 42(25.5) | 55(33.3) | 43(26.1) | 55(33.1) | <0.001 |
| Hypertension | 41(24.8) | 32(19.4) | 44(26.7) | 47(28.3) | 0.262 |
| Hyperlipidemia | 46(27.9) | 73(44.2) | 76(46.1) | 80(48.2) | <0.001 |
| Drinking | 56(33.9) | 47(28.5) | 50(30.3) | 53(31.9) | 0.742 |
| Smoking | 34(20.6) | 32(19.4) | 38(23) | 43(25.9) | 0.198 |
| Aerobic exercise | 43(26.1) | 52(31.5) | 54(32.7) | 46(27.7) | 0.504 |
| Education(>12years) | 33(20.0) | 41(24.8) | 31(18.8) | 24(14.5) | 0.123 |
| MCI | 6(3.6) | 14(8.5) | 28(17.0) | 32(19.3) | <0.001 |

| | | | | | |
|---|---|---|---|---|---|
| | | Mean(SD) | | | |
| Age (year) | 47.4(6.9) | 47.5(7.3) | 49.1(7.5) | 50.2(6.9) | <0.001 |
| BMI(kg/m2) | 26.1(3.4) | 26.1(3.6) | 26.5(3.5) | 26.2(3.9) | 0.712 |
| WHR | 0.89(0.08) | 0.89(0.08) | 0.89(0.07) | 0.89(0.06) | 0.903 |
| Total energy | 1830612) | 1815(675) | 2365(871) | 2197(735) | <0.001 |
| Intake (% of energy) | | | | | |
| % Carbohydrate | 68(5) | 59(4) | 51(3) | 38(7) | <0.001 |
| % Protein | 16(3) | 17(3) | 17(2) | 18(4) | <0.001 |
| | | | | | |
| Intake (g/d) | | Median(Q75-Q25) | | | |
| Carbohydrate | 278(170) | 252(215) | 291(141) | 200(131) | <0.001 |
| Protein | 62(37) | 74(40) | 97(58) | 96(51) | <0.001 |
| Fat | 28(15) | 47(24) | 76(49) | 103(63) | <0.001 |
| Fiber | 10(9.2) | 12(9.1) | 15(8.3) | 14(10.6) | <0.001 |

Abbreviations: MCI, mild cognitive impairment; SD, Standard Deviation; Q, Quartiles; BMI, body mass index; WHR, waist-to-hip ratio

Table 3. Risk factor of MCI by Logistic Regression Analysis

| Variable | wald | OR | 95%CI | *P* |
|---|---|---|---|---|
| BMI* | 2.828 | 1.36 | 0.95-1.96 | 0.09 |
| Age* | 7.846 | 1.72 | 1.18-2.52 | 0.005 |
| Hypertension | 0.257 | 1.15 | 0.62-2.02 | 0.61 |
| Hyperlipidemia | 12.071 | 2.46 | 1.48-4.10 | 0.001 |
| Diabetes | 0.308 | 1.17 | 0.68-2.02 | 0.58 |
| Education* | 4.677 | 0.54 | 0.31-0.94 | 0.031 |
| Energy (quartiles) | 17.251 | 1.67 | 1.31-2.12 | <0.001 |

Abbreviations: CI, confidence interval; OR, odds ratio; MCI, mild cognitive impairment; BMI, body mass index.

*Processing as Classification variables, BMI (<25,25-29.9, ≥ 30), age(<45,45-55,>55), education(≤ 6,6-12,>12)

Table 4. Association of % macronutrients (carbohydrates, fat, and protein) with incidence of MCI

| Variable | Cut point(%) | Incident MCI,N(%) | OR (95%CI)[a] | *P* |
|---|---|---|---|---|
| Carbohydrate | | | | |
| Q1 | <46 | 33(20.0) | reference | |
| Q2 | 47-54 | 25(15.2) | 0.77(0.42-1.41) | 0.39 |
| Q3 | 55-63 | 15(9.1) | 0.58(0.29-1.16) | 0.12 |

| | | | | |
|---|---|---|---|---|
| Q4 | >63 | 7(4.2) | 0.30(0.12-0.72) | 0.007 |
| Protein | | | | |
| Q1 | <14.9 | 10(6.1) | reference | |
| Q2 | 15.0-16.5 | 20(12.1) | 1.70(0.74-3.93) | 0.21 |
| Q3 | 16.6-18.5 | 23(13.9) | 2.48(1.09-5.61) | 0.03 |
| Q4 | >18.5 | 27(16.3) | 2.77(1.24-6.15) | 0.01 |
| Fat | | | | |
| Q1 | <20 | 6(3.6) | reference | |
| Q2 | 21-28 | 14(8.5) | 2.22(0.81-6.10) | 0.12 |
| Q3 | 29-35 | 28(17.0) | 3.36(1.30-8.67) | 0.01 |
| Q4 | >35 | 32(19.3) | 3.90(1.53-9.89) | 0.004 |

Abbreviations: CI, confidence interval; OR, odds ratio; MCI, mild cognitive impairment

Adjusted for age, BMI, Education, energy (Quartiles), Hyperlipidemia

**STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies***

| Section/Topic | Item # | Recommendation | Reported on page # |
|---|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | 2 |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | 2 |
| **Introduction** | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | 3 |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | 3 |
| **Methods** | | | |
| Study design | 4 | Present key elements of study design early in the paper | 3 |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 3,4 |
| Participants | 6 | (*a*) Give the eligibility criteria, and the sources and methods of selection of participants | 4 |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 4,5 |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | 4,5 |
| Bias | 9 | Describe any efforts to address potential sources of bias | *10* |
| Study size | 10 | Explain how the study size was arrived at | 3 |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | 4,5 |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | 6 |
| | | (*b*) Describe any methods used to examine subgroups and interactions | 6 |
| | | (*c*) Explain how missing data were addressed | N/A |
| | | (*d*) If applicable, describe analytical methods taking account of sampling strategy | 6 |
| | | (*e*) Describe any sensitivity analyses | N/A |
| **Results** | | | |

| | | | |
|---|---|---|---|
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | 3 |
| | | (b) Give reasons for non-participation at each stage | 3 |
| | | (c) Consider use of a flow diagram | |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | 6 |
| | | (b) Indicate number of participants with missing data for each variable of interest | N/A |
| Outcome data | 15* | Report numbers of outcome events or summary measures | 6 |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | 6，7 |
| | | (*b*) Report category boundaries when continuous variables were categorized | 6.7 |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | 6.7 |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | N／A |
| **Discussion** | | | |
| Key results | 18 | Summarise key results with reference to study objectives | 8 |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | 10 |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | 10 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | 10 |
| **Other information** | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | 11 |

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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# The association between macronutrient intake and cognition in individuals aged under 65 in China: A cross sectional study



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| | |

**The association between macronutrient intake and cognition in individuals aged under 65 in China: A cross sectional study**

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**Abstract**

**Objective:** The aim of this retrospective study was to explore the correlation between daily energy intake from macronutrients and cognitive functions in Chinese population aged less than 65 years.

**Design**: This is a cross sectional study to explore the relationships between macronutrients intake and cognitive function. The Analysis of Variance (ANOVA) and $\chi^2$ test were used to compare the demographic and physical characteristics, lifestyle, and laboratory parameters with the intake of macronutrients among different quartiles of % fat/energy. Multivariate logistic regression analysis was applied to identify the potential risk factors of mild cognitive impairment (MCI).

**Subjects**: Young and middle-aged subjects (age<65 years) were recruited from Beijing, China. The Montreal cognitive assessment (MoCA) and Mini-mental state examination (MMSE) were used to evaluate the cognitive functions, and the dietary intake of the subjects' was estimated with a semi-quantitative food frequency questionnaire (FFQ).

**Results:** Among the661 subjects,80(12.1%) had MCI, while 581(87.9%) had normal cognitive functions. On evaluating the data based on the age group, educational background, and conditions of hyperlipidemia and total energy intake, the results revealed that high % fat (upper quartile: adjusted odds ratio [aOR] 3.90, 95% confidence interval [CI] 1.53-9.89, *p*=0.004), and high % protein intake (upper quartile:aOR2.77, 95%CI 1.24-6.15) were greatly associated with increased frequency of MCI, while high % carbohydrate intake (upper quartile:aOR0.30, 95%CI 0.12-0.72) was correlated with decreased prevalence of MCI.

**Conclusion:** The dietary pattern with high percentage of energy intake from fat and protein, and low energy intake from carbohydrate might have associated with cognitive decline in Chinese population under 65 years of age.

**Key words:** Dietary pattern; mild cognitive impairment; macronutrients; energy intake

**Strengths and limitations of this study**

1. This study is a cross sectional study to explore intake of macronutrients in dietary and cognition of in Chinese people.

2. Compared to the previously published studies, this study involved relatively younger subjects aged less than 65 to minimize the influence of age on cognition.

3. The Montreal cognitive assessment (MoCA) and Mini-mental state examination (MMSE) were both employed to evaluate the cognitive functions of participants.

4. The limitation of this study was there was no report on the breakdown of dietary fat consumption because different sources of fat maybe have different effect on cognitive.

## Introduction

Macronutrients including fat, protein and carbohydrate are the main sources of dietary energy, and a high-energy intake may increase the risk of cognitive impairment. Dietary pattern and intake of nutrients have been shown to be associated with cognitive functions[1, 2]. Mediterranean diet (MD), rich in fresh vegetables, fruits, fish and olive oil, has been reported to have associations with declined cognitive functions[3, 4]. Similarly, two earlier studies of our research group have previously demonstrated that diet rich in marine products, fruits, vegetables and vegetable juice could prevent cognitive decline in the elderly population[5, 6]. Moreover, it was demonstrated that the long-chain omega-3 fatty acids (LC-n3-FA) and polyphenols including resveratrol, curcuminand flavonoids from these diets are likely the main nutrients beneficial to cognitive function[4, 7]. Some previous study has reported that adequate dietary intake of vitamins and minerals were closely associated with decreased risk of cognitive impairment[8]. However, those studies could examine only the cumulative effects of different foods and micronutrients, without considering the influence of energy intake and the source of energy as a possible risk factor in developing mild cognitive impairment (MCI). A prospective cohort study[9]reported that the high average energy consumption could increase the risk of cognitive impairment or dementia (OR:1.62, 95% CI:1.25-2.10), after analyzing the factors like micronutrients, vascular disease, diabetes, smoking, BP and BMI, but this study include the differential sources of energy intake.

The primary determinants of total caloric intake and the largest proportion of the components of any diet include the three types of macronutrients: carbohydrates, fat and protein. The balanced ratio of carbohydrates, fat and protein was the basis of healthy diets, which ensures adequate intake of all nutrients. Up to now, however, there were limited studies that investigated the significant affect of macronutrient (carbohydrates, fat and protein) with cognitive function. Roberts*et al.*[10] have reported that a relatively high caloric intake from carbohydrates might increase the risk of MCI or dementia in elderly persons. Due to the inherent differences in Western and Chinese diets, this conclusion may not significantly apply to Chinese population. Thus, we conducted a case-control study to explore the relationship between macronutrients and energy intake and cognitive functions in a cohort of Chinese population less than 65 years of age to control the bias of aging.

## Methods

**Subjects**

This retrospective study was conducted in three community hospitals in Beijing, during December 1, 2015 to September 30, 2016.We identified 1197 (age<65) potentially eligible subjects out of 4360outpatients, and 777among them agreed to participate (64.9%responserate) in the study. Finally, 661 participants were included in the study according to the exclusion criteria: individuals with serious diseases (cancer, severe psychiatric disorders such as depression and schizophrenia, a recent history of heart or respiratory failure and chronic liver or renal failure, n=25);individuals with conditions known to affect cognitive functions(a recent history of alcohol abuse, n=43;cerebral infarction, n=27; severe brain injury, n=3);individuals with Alzheimer's disease (AD)(n=0), Parkinson's disease(PD) (n=0) or long-term frequent intake of anti-depressants and other medications for neurological diseases (n=18). All experimental procedures were conducted in accordance with the guidelines in the Declaration of Helsinki and approved by the Ethics Committee of Capital Medical University, Beijing (No.2014SY33). All participants signed a written informed consent and had the right to terminate their participation at their willing.

**Data collection and grouping**

Questionnaire including demographic characteristics and lifestyle was prepared and the data was collected and assessed by well-trained researchers by conducting face-to-face interviews. The collected data by questionnaire included age, gender, education, race/ethnicity(divided into Han and other, including Manchu, Hui, Koreans, Mongols and so forth), work intensity, smoking (yes or no), drinking (yes or no), physical exercise, and disease history (hypertension, diabetes, and so forth). Height and weight were measured with height and weight scales (RGZ-120-RT,Wuxi weighing apparatus factory).Waist and hip circumferences were measured by flexible rulers, and Waist-to-Hip Ratio (WHR) was calculated as waist circumference (cm) / hip circumference (cm). Blood samples were collected for quantifying the lipid levels (total cholesterol and triglyceride) with an auto-analyzer (Olympus, AU 400, Japan). Hyperlipidemia was defined as hypercholesterolemia (serum cholesterol>5.2mmol/L) and/or hypertriglyceridemia (serum triglyceride>1.7 mmol/L).

Age was categorized into three groups: <45 years old, 45~55 years old and >55 years old. Body mass index(BMI)was calculated as weight(kg)/height$^2$($m^2$) and subsequently divided into three groups[11, 12]: normal (18.5~24.9 kg/$m^2$), overweight (25.0~29.9 kg/$m^2$) and obese (⩾30 kg/$m^2$).

Educational levels were divided into three ranks[13]: ≤ 6 years (illiterate and elementary school), 7~12 years (junior high school, senior high school and technical secondary school) and > 12 years (college and graduate school). Work intensity which was estimated based on their profession was categorized into three groups[14]: light (75% of time sitting or standing and 25% of time standing with activities, such as office workers, salesman and teacher), moderate (25% of time sitting or standing and 75% of time with special occupational activities, e.g. students daily activities, motor vehicle driving, metalworking and electrical installation), and heavy (40% of time sitting or standing and 60% of time with special occupational activities, e.g. weeding, weight-bearing walking, dancing, skiing, riding a bicycle, mountain climbing, logging, manual excavation, playing basketball and football).Aerobicexercise[15] refers to physical exercise of low to high intensity, including running/jogging, climbing, jumping rope, brisk walking, swimming andplaying badminton.

**Dietary questionnaire**

Dietary intake was estimated by using a semi-quantitative food frequency questionnaire (FFQ)[816], which included a total of 34 items (whole grain, red meat, pork, beef, mutton, chicken, fish, legume and legume product, milk, eggs, fruits and vegetables, nuts, sugared beverages, cooking oil, etc.), consumption frequency (daily, weekly, monthly, yearly or never)and the quantity of each item consumed. The quantity of food consumed was estimated using food models and measuring rulers or cups. Subsequently, the intake of nutrients per day was calculated based on the China Food Composition Database[17]. Trained dietary interviewers helped all participants in completing the FFQ to make sure the accuracy of the collected data.

**Cognitive function screening for MCI**

The Montreal cognitive assessment (MoCA) and Mini-mental state examination (MMSE) were employed to evaluate the cognitive functions of participants according to the standard protocols. The total scores of MoCA was 30 and the cut-off for screening MCI was13 for illiterate individuals, 19 for individuals with 1-6 years of education, and 24 for individuals with 7 or more years of education as previously described[8]. The total scores of MMSE was 30, and the cut-off scores for screening MCI were as follows: 19 for illiterate individuals, 22 for individuals with 1-6 years of education and 26 for individuals with 7 or more years of education. These criteria we

followed have been proven to be appropriate for screening MCI in elderly Chinese people in a large cohort-based study[18].The screening of MCI in the present study was a combination of these two methods with the following criteria: MoCA≤13 and MMSE≥20 for illiteracy; MoCA≤ 19 and MMSE≥ 23 for subjects with 1-6 years of education; MoCA≤ 24 and MMSE≥27 for subjects with ≥7 years of education.

**Statistical analysis**

Statistical analyses were performed using the SPSS 17.0 software (SPSS Inc., Chicago, IL, USA). Data was tested for normality distribution by visual inspection of histograms and the Shapiro-Wilk W-test. Continuous variables were presented as mean ± standard deviation (SD) or Median (Q), and categorical variables were described as frequencies (percentage). Logistic regression analysis was used to compare the demographic characteristics, lifestyle and physical and laboratory parameters between subjects with and without MCI.The Analysis of Variance (ANOVA) and rank sum test forcontinuousvariablesandCochran-Mantel-Haenszel$\chi^2$ test for categorical variables were used to compare the demographic characteristics, lifestyle, physical and laboratory parameters and macronutrients intake among different quartiles of % fat/energy (percentage of energy from total fat).Multivariate logistic regression was used to identify the potential risk factors of MCI and to estimate the risk of MCI between different quartiles of %nutrients/energy (percentage of energy from each nutrient). All statistical analyses were performed with a two-tailed alpha level of 0.05.

**Results**

**Demographic and physical characteristics of subjects**

A total of 661 subjects were included in this study. The demographic and physical characteristics, lifestyle, and laboratory parameters and their association with MCI were presented in Table 1. Of all the subjects, 303 (45.8%) were males and 358 (54.2%) were females; the average age was 48.5 ± 7.3 years (30~64 years); the average BMI was 26.2 ± 3.6 kg/m$^2$; the overweight and obese group included 310 (46.9%) and 104 (15.7%), respectively; 80(12.1%) subjects had MCI and the other 581 participants (87.9%) had normal cognitive functions. Increased age and BMI, and the presence of hypertension and hyperlipidemia were associated with greater prevalence of MCI, while educational level was negatively correlated with the prevalence

of MCI. However, other factors such as gender, race/ethnicity, labor intensity, aerobic exercise, smoking, drinking, diabetic and hypertension status were not associated with the prevalence of MCI (Table1).

We next compared the demographic characteristics, lifestyle, physical and laboratory parameters and energy intake from each macronutrient across quartiles of % fat/energy (percentage of energy from total fat). As shown in table 2, subjects in higher % fat/energy quartiles had shown increased frequency of MCI, with diabetes and hyperlipidemia at more advanced age. Lifestyle (smoking, drinking and exercise) and BMI were not significantly different across quartiles of % fat/energy. The total energy intake in the highest % fat/energy quartile was higher than that in the lowest quartile, but lower than that in the third % fat/energy quartile. Intake of protein and dietary fiber (in term of g/day or % of total energy) was increased across increasing % fat/energy quartiles, while the intake of carbohydrates was decreased as quartiles of % fat/energy raised. These data suggested that the increased dietary intake of fat might be associated with the development of MCI.

Before analysis of the relationship between macronutrients intake and cognitive function, a multivariate logistic regression analysis was employed to identify the association of BMI, age, education, hypertension, hyperlipidemia, diabetes and energy intake with MCI. In this assay, MCI status was defined as the dependent variable, while BMI, age, education, hypertension, hyperlipidemia, diabetes and energy intake were set as the independent variables. As shown in table 3, age (OR 1.72, 95% CI 1.18-2.52), hyperlipidemia(OR 2.46, 95% CI 1.48-4.10) and total energy intake(OR1.67,95%CI1.31-2.12) were positively associated with the risk for MCI, while education(OR0.54,95%CI0.31-0.94) was a protective factor for MCI. Although BMI was not significantly associated with the risk for MCI, a trendexhibiting increased risk of MCI was observed in subjects with higher BMI (OR1.36,95%CI0.95-1.96).

We then explored the association of% of energy from a specific macronutrient (carbohydrates, fat and protein) on the prevalence of MCI, with their age, BMI, education, energy (quartiles) and hyperlipidemia. The risk of MCI was reduced by about 70%in the highest quartile of %

carbohydrate/energy group. On the contrary, the risk for MCI was increased to nearly 2.48 and 2.77 fold in the third and the highest quartile of % protein/energy, respectively. In consistence, the risk for MCI was elevated to around 3.36 and 3.90 fold in the third and the highest quartile of % fat/energy, respectively (Table 4).

**Discussion**

This study involving young and middle-age group population showed that a higher % fat/energy and % protein/energy intakes were associated with an increased prevalence of MCI. In contrast, a high % carbohydrate/energy intake was correlated with a reduced risk of MCI. These findings suggested that a dietary pattern of high fat and protein intake and a low carbohydrate intake might have adverse effects on the development of MCI. Therefore, a balanced dietary pattern that consists of optimal fat, protein and carbohydrate proportions may be beneficial to maintain normal cognitive function in this population.

Our findings were contrary to the results of a study by Robert *et al.*, which reported that diet with a relatively high caloric intake from carbohydrates and a low caloric intake from fat and proteins might increase the risk of MCI[10]. This inconsistency may stem from the difference in the age of subjects and the differential source of carbohydrate in their diets. In the present study, the participants were relatively younger than the subjects in the studyby Robert *et al.* (<65years VS 70-89 years).In addition, Chinese diets are rich in starchy foods (e.g., refined grain, tubers and their products), which might represent the main source of dietary energy, while carbohydrates in Robert*et al.* study were mainly derived from simple sugars. As we know, elderly persons having a dietary pattern high in simple sugars may often disrupt the normal glucose and insulin metabolism[19-22]. Glucose and insulin metabolism has been shown to have a close relationship with cognitive functions[23]. Therefore, we hypothesized that in the study by Robert*et al.,* ahigh level of simple sugar intake was a potential risk factor of MCI in the elders (median age = 79.5 years). In our study, the participants were much younger (48.5 ± 7.3 years) and obtained carbohydrates mainly from starchy foods, thus their risk of abnormal blood glucose level and insulin metabolism was minimal and they consequently showed a lower prevalence of MCI. Collectively, we speculated that intake of high fat instead of high carbohydrates might represent a key dietary factor for increased risk of MCI in younger population.

The association between fat intake and MCI has been well established by conducting a series of human and rodent studies. A randomly controlled clinical trial has shown that attention, speed and mood were impaired in a cohort of young males (aged 22±1 years) subjected to high-fat, low-carbohydrate diets for 5 days[24], suggesting that a high-fat diet was potentially detrimental to the brain in healthy subjects. Edwards *et al.* had demonstrated that consumption of a high-fat diet led to increased simple reaction time and decreased power of attention[25]. Moreover, in animal studies, rats fed with long-term high-fat diet developed hippocampal microvascular insulin resistance and significantly declined cognitive function in the two-trial spontaneous alternation behavior test and the novel object recognition test[26]. In addition, a high fat diet (40% energy from fat) had shown to induce biochemical changes (increased amyloid beta deposition and neurofibrillary tangle formation) and decreased synaptic plasticity in the brain of mice[26, 27].

As suggested by the human and animal studies, the effect of high fat intake on MCI might have resulted due to insulin resistance (IR). High fat diet is regarded as a well-established approach to induce IR in peripheral organs and hypothalamus[27, 28]. Accumulating evidence has shown that a high fat diet could cause increased blood glucose levels and free fatty acid (FFA) concentrations [29], and subsequent insulin insensitivity. However, the relationship between cognitive function and insulin sensitivity/resistance has been well established by conducting many studies [30-33]. Therefore, we assumed that a similar mechanism might have accounted for the increased risk of MCI caused by high fat intake in this present study. We also found that hyperlipidemia(hypercholesterolemia and/or hypertriglyceridemia) was associated with the risk for developing MCI. But the relationship among hyperlipidemia, increased fat intake and cognitive impairment is still unclear. A systematic review and meta-analysis[34]showed that, the reduction in triglyceride levels was more distinct in the high-fat diet groups. Holloway *et al.*[24]have reported that there is no significant difference in cholesterol concentrations between high-fat diet and standard diet groups. Thus hyperlipidemia was not necessarily a result of high fat intake, and it might be independent of the high-fat diet-induced risk of MCI.

Interestingly, we have noticed that the prevalence of MCI was higher as the protein intake was increased (table 4). In china, during recent years, the intake of dietary protein among population has increased, and the main sources of protein have changed from vegetable proteins to animal proteins, in particular the red meats [35]. We speculated that, when protein

accounts for only 15.0%-16.5% of total energy, the protein intake might not show any significant association with the incidence of MCI. Moreover, it suggests that an appropriate protein intake is critical for maintaining normal cognitive functions and that over-consumption of protein might be harmful to cognition. However, the appropriate protein intake for optimal cognitive functions and the ways to delay the decline in cognition with advanced age remained unknown [36].

In addition to macronutrients intake, we identified other potential risk factors for the development of MCI in this study, including age, education, hyperlipidemia and total energy intake. Aging has been associated with an increased risk of cardiovascular diseases and Alzheimer's disease, which is manifested by reduced cognitive function, neuro-degeneration and the onset of dementia[37]. In consistence with a previous study, advanced age was associated with a decline in cognitive function in the present study. Moreover, we found that hyperlipidemia was associated with significantly increased risk of MCI (OR 2.46, $p<0.01$), as reported by other studies [38, 39]. Educational attainments is a key component of successful maintenance of cognitive function in old people, and thus serve as a major protective factor for dementia [40].Consistently, we found that higher educational level was potentially a protective factor against MCI in this study. In addition to these demographic characteristics, we also discovered that a high total energy intake was significantly correlated with increased risk of MCI. Consequent with an energy intake increase during each quartile, the risk of MCI was increased by around 1.66 folds (Table 3). However, this increased risk was not associated with overweight and obesity, since we didn't find any significant difference in BMI and WHR among energy intake quartiles. Moreover, after adjusted for energy intake, the results demonstrated that high fat and protein intake was associated with increased risk of MCI (table 4).

There were some limitations of this study. Firstly, being a retrospective study,recall bias in reporting of dietary nutrients could not be excluded, especially for those with cognitive impairment. To effectively minimize the potential recall bias, we used special model and measuring rulers or cups to help in quantifying the consumed food. Secondly, as the subjects were recruited at community hospitals, the study exhibited a potential risk for participation bias. Moreover, the higher frequencies of vascular disease risk factors (such as diabetes, hypertension and hyperlipidemia) in participants, might introduce bias towards the association between

dietarynutrients intake and cognitive function. Thirdly, hypertension and diabetes were self-reported, which might introduce information bias. Finally, the participants were recruited only from Beijing, and any generalization of the results of this study to other locations and to other ethnicities should be performed with cautions.

In summary, after adjusted for age, education, hyperlipidemia and total energy intake, high fat and protein intake and low carbohydrate intake were associated with greater risk for MCI. A balanced dietary pattern consisting of optimal fat, protein and carbohydrate ratio may be potentiallybeneficial to the maintenance of normal cognitive functions in young and middle-aged people.

**Authorship**

WWM and RX conceived and designed the study, YZ and BJD collected the data, BJD performed the statistical analyses and drafted the manuscript, LZ drafted and revised the manuscript, and YXB helped in collection and analysis of the data. All authors read and approved the final manuscript.

**Ethics declaration**

All experimental procedures were conducted in accordance with the guidelines in the Declaration of Helsinki and approved by the Ethics Committee of Capital Medical University, Beijing(No.2014SY33).

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**Data sharing statement**

The materials and datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Conflict of Interest**

None

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Table 1.MCI by different groups of characteristics

| Variables | N(%) | Means(SD) | OR(95%CI) | *P* value |
|---|---|---|---|---|
| Total | | | | |
| Sex | | | | |
| Male | 303(45.8) | | reference | |
| Female | 358(54.2) | | 1.57(0.98-2.55) | 0.068 |
| Age(years) | | 48.5±7.3 | | |
| <45 | 213(32.2) | | reference | |
| 45~55 | 286(43.3) | | 3.69(1.75-7.78) | 0.001 |
| >55 | 162(24.5) | | 5.36(2.47-11.63) | <0.001 |
| BMI(kg/m$^2$) | | 26.2±3.6 | | |
| <25 | 247(37.4) | | reference | |
| 25~29.9 | 310(46.9) | | 2.33(1.32-4.12) | 0.004 |
| ≥ 30 | 104(15.7) | | 1.98(0.94-4.15) | 0.071 |
| WHR | | | | |
| Normal | 261(39.5) | | reference | |
| Abnormal* | 400(60.5) | | 1.04(0.64-1.67) | 0.886 |
| Race/ethnicity | | | | |
| Han | 608(92.0) | | reference | |
| Other | 53(8.0) | | 0.92(0.38-2.23) | 0.856 |
| Education(years) | | | | |
| ≤ 6 | 51(7.7) | | reference | |
| 7~12 | 481(72.8) | | 0.64(0.31-1.34) | 0.238 |
| > 12 | 129(19.5) | | 0.17(0.05-0.51) | 0.002 |
| Labor intensity | | | | |
| Light | 508(76.9) | | reference | |
| Moderate | 133(20.1) | | 1.37(0.31-6.03) | 0.679 |
| Hard | 20(3.0) | | 0.81(0.17-3.96) | 0.796 |

| | | | |
|---|---|---|---|
| Aerobic exercise | | | |
| NO | 466(70.5) | reference | |
| YES | 195(29.5) | 0.83(0.49-1.41) | 0.497 |
| Smoking | | | |
| NO | 514(77.8) | reference | |
| YES | 147(22.2) | 1.49(0.88-2.51) | 0.137 |
| Drinking | | | |
| NO | 455(68.9) | reference | |
| YES | 206(31.1) | 0.52(0.29-0.92) | 0.027 |
| Diseases history | | | |
| Hypertension | | | |
| NO | 497(75.2) | reference | |
| YES | 164(24.8) | 1.76(1.07-2.90) | 0.026 |
| Diabetes | | | |
| NO | 466(70.5) | reference | |
| YES | 195(29.5) | 0.85(0.52-1.41) | 0.531 |
| Hyperlipidemia | | | |
| NO | 386(58.4) | reference | |
| YES | 275(41.6) | 2.80(1.73-4.55) | <0.001 |
| MCI | | | |
| NO | 581(87.9) | | |
| YES | 80(12.1) | | |

Abbreviations: CI, confidence interval; OR, odds ratio; SD, Standard Deviation; BMI, body mass index; WHR, waist-to-hip ratio, MCI, mild cognitive impairment
*WHR >0.8 for female, WHR>0.9 for male.

Table 2.Characteristics of subjects by % fat intake

| Variable | Quartiles of% fat of total energy | | | | *P* value |
|---|---|---|---|---|---|
| | Q1 <20% N=165 | Q2 20-28% N=165 | Q3 29-35 N=165 | Q4 >35% N=165 | |
| | | N (%) | | | |
| Female | 95(57.6) | 88(53.3) | 93(56.4) | 82(49.4) | 0.447 |
| Diabetes | 42(25.5) | 55(33.3) | 43(26.1) | 55(33.1) | <0.001 |
| Hypertension | 41(24.8) | 32(19.4) | 44(26.7) | 47(28.3) | 0.262 |
| Hyperlipidemia | 46(27.9) | 73(44.2) | 76(46.1) | 80(48.2) | <0.001 |
| Drinking | 56(33.9) | 47(28.5) | 50(30.3) | 53(31.9) | 0.742 |
| Smoking | 34(20.6) | 32(19.4) | 38(23) | 43(25.9) | 0.198 |
| Aerobic exercise | 43(26.1) | 52(31.5) | 54(32.7) | 46(27.7) | 0.504 |
| Education(>12years) | 33(20.0) | 41(24.8) | 31(18.8) | 24(14.5) | 0.123 |
| MCI | 6(3.6) | 14(8.5) | 28(17.0) | 32(19.3) | <0.001 |
| | | Mean(SD) | | | |
| Age (year) | 47.4(6.9) | 47.5(7.3) | 49.1(7.5) | 50.2(6.9) | <0.001 |

| | | | | | |
|---|---|---|---|---|---|
| BMI(kg/m2) | 26.1(3.4) | 26.1(3.6) | 26.5(3.5) | 26.2(3.9) | 0.712 |
| WHR | 0.89(0.08) | 0.89(0.08) | 0.89(0.07) | 0.89(0.06) | 0.903 |
| Total energy | 1830612) | 1815(675) | 2365(871) | 2197(735) | <0.001 |
| Intake(% of energy) | | | | | |
| % Carbohydrate | 68(5) | 59(4) | 51(3) | 38(7) | <0.001 |
| % Protein | 16(3) | 17(3) | 17(2) | 18(4) | <0.001 |
| | | | | | |
| Intake(g/d) | | Median(Q75-Q25) | | | |
| Carbohydrate | 278(170) | 252(215) | 291(141) | 200(131) | <0.001 |
| Protein | 62(37) | 74(40) | 97(58) | 96(51) | <0.001 |
| Fat | 28(15) | 47(24) | 76(49) | 103(63) | <0.001 |
| Fiber | 10(9.2) | 12(9.1) | 15(8.3) | 14(10.6) | <0.001 |

Abbreviations: MCI, mild cognitive impairment; SD, Standard Deviation; Q, Quartiles; BMI, body mass index; WHR, waist-to-hip ratio

Table 3. Risk factor of MCI by Logistic Regression Analysis

| Variable | wald | OR | 95%CI | *P* |
|---|---|---|---|---|
| BMI* | 2.828 | 1.36 | 0.95-1.96 | 0.09 |
| Age* | 7.846 | 1.72 | 1.18-2.52 | 0.005 |
| Hypertension | 0.257 | 1.15 | 0.62-2.02 | 0.61 |
| Hyperlipidemia | 12.071 | 2.46 | 1.48-4.10 | 0.001 |
| Diabetes | 0.308 | 1.17 | 0.68-2.02 | 0.58 |
| Education* | 4.677 | 0.54 | 0.31-0.94 | 0.031 |
| Energy (quartiles) | 17.251 | 1.67 | 1.31-2.12 | <0.001 |

Abbreviations: CI, confidence interval; OR, odds ratio; MCI, mild cognitive impairment; BMI, body mass index.

*Processing as Classification variables,BMI (<25,25-29.9, ≥ 30), age(<45,45-55,>55),education(≤ 6,6-12,>12)

Table 4. Association of % macronutrients (carbohydrates, fat, and protein) with incidence of MCI

| Variable | Cutpoint(%) | Incident MCI, N(%) | OR(95%CI)[a] | *P* |
|---|---|---|---|---|
| Carbohydrate | | | | |
| Q1 | <46 | 33(20.0) | reference | |
| Q2 | 47-54 | 25(15.2) | 0.77(0.42-1.41) | 0.39 |
| Q3 | 55-63 | 15(9.1) | 0.58(0.29-1.16) | 0.12 |
| Q4 | >63 | 7(4.2) | 0.30(0.12-0.72) | 0.007 |
| Protein | | | | |

| | | | | |
|---|---|---|---|---|
| Q1 | <14.9 | 10(6.1) | reference | |
| Q2 | 15.0-16.5 | 20(12.1) | 1.70(0.74-3.93) | 0.21 |
| Q3 | 16.6-18.5 | 23(13.9) | 2.48(1.09-5.61) | 0.03 |
| Q4 | >18.5 | 27(16.3) | 2.77(1.24-6.15) | 0.01 |
| Fat | | | | |
| Q1 | <20 | 6(3.6) | reference | |
| Q2 | 21-28 | 14(8.5) | 2.22(0.81-6.10) | 0.12 |
| Q3 | 29-35 | 28(17.0) | 3.36(1.30-8.67) | 0.01 |
| Q4 | >35 | 32(19.3) | 3.90(1.53-9.89) | 0.004 |

Abbreviations: CI, confidence interval; OR,odds ratio; MCI, mild cognitive impairment

Adjusted for age, BMI, Education, energy(Quartiles),Hyperlipidemia

**STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies***

| Section/Topic | Item # | Recommendation | Reported on page # |
|---|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | 2 |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | 2 |
| **Introduction** | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | 3 |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | 3 |
| **Methods** | | | |
| Study design | 4 | Present key elements of study design early in the paper | 3 |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 3,4 |
| Participants | 6 | (*a*) Give the eligibility criteria, and the sources and methods of selection of participants | 4 |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 4,5 |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | 4,5 |
| Bias | 9 | Describe any efforts to address potential sources of bias | *10* |
| Study size | 10 | Explain how the study size was arrived at | 3 |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | 4,5 |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | 6 |
| | | (*b*) Describe any methods used to examine subgroups and interactions | 6 |
| | | (*c*) Explain how missing data were addressed | N/A |
| | | (*d*) If applicable, describe analytical methods taking account of sampling strategy | 6 |
| | | (*e*) Describe any sensitivity analyses | N/A |
| **Results** | | | |

| | | | |
|---|---|---|---|
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | 3 |
| | | (b) Give reasons for non-participation at each stage | 3 |
| | | (c) Consider use of a flow diagram | |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | 6 |
| | | (b) Indicate number of participants with missing data for each variable of interest | N/A |
| Outcome data | 15* | Report numbers of outcome events or summary measures | 6 |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | 6，7 |
| | | (*b*) Report category boundaries when continuous variables were categorized | 6.7 |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | 6.7 |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | N／A |
| **Discussion** | | | |
| Key results | 18 | Summarise key results with reference to study objectives | 8 |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | 10 |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | 10 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | 10 |
| **Other information** | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | 11 |

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.